THE MEDICAL CLINICS OF NORTH AMERICA

JANUARY 1974

ALLERGY IN ADULTS

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SYMPOSIUM ON
ALLERGY IN ADULTS: Review and Outlook

Max Samter, M.D., *Guest Editor*

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Foreword

MAX SAMTER, M.D.

The title of this volume implies that it has been conceived as a "practical" volume: patients must be treated, and treated well. The participants of the symposium have agreed to include in their contributions approaches to diagnosis and treatment which have stood the test of time and should be retained; approaches which have failed to live up to critical evaluation and should be discarded; and approaches which hold promise but might not have been sufficiently tested to date to merit unrestrained approval.

It will become apparent to our readers that we are headed toward profound changes in the direction of the specialty. The "classical diseases" of allergy—so steeped in clinical know-how, so well described, so familiar—have managed to raise a host of new questions which contribute to our interpretation of nonclassical allergies as well; and of the eventual tissue injury which determines the clinical presentation of both.

Some articles, such as that of Dr. Smith on the epidemiology of atopic diseases or that of Dr. Cohn on genetics, are examples of how far we have yet to go. Genetics emerges as one of the strong formative forces in allergy and should become a firm link between classical allergists and the new breed of clinical immunologists who will tackle anything as long as an antibody is involved in it. Like statistics, genetics is still behind the scenes, but if it maintains its current pace, it will be able to extend its scope from the identification of the genetic behavior of large groups to the identification of individual problems which are still, more often than not, beyond solution.

Seasonal and perennial allergic rhinitis used to be considered "simple" allergic diseases, but there is no doubt that our notion that IgE-mediated diseases are simple must be given up, at least for the time being; and bronchial asthma might turn out to be three or four separate diseases which have a final effector tissue in common.

The same is true for urticaria, but recent proposals for its classification have been so extravagant that their clinical usefulness has seriously suffered. Dr. Mathews has re-emphasized the central role of the mast cell as target tissue for multiple forms of injury as the central although prefinal effector organ in the pathogenesis of urticaria, similar to the role assigned to cyclic AMP in the pathogenesis of bronchial asthma. It seems likely that the low yield of etiologic diagnoses in urticaria and angioedema which Dr. Mathews reports is the direct result of our carefree use of chemicals to which we are exposed without knowing it: this might not change until more stringent laws for labelling foods and drugs have been passed, and enforced.

In recent years, interest in the skin as a target tissue for virtually every type of allergic reaction has been sustained and informative. The article on the allergic reactions of the skin (other than urticaria) does away with the myth that the integument has only a limited capacity to participate in immunological reactions; and ascertains that most immunological reactions of the skin can be precisely identified.

It is intriguing that an entire article in a volume on "Allergies in Adults" deals with diseases which simulate allergies. Only a short while ago it was necessary to persuade the house staff of almost every major hospital that diseases of uncertain etiology might be immunologic diseases. Our persuasion has been so successful – with the trend of the times on our side – that residents now tend to suspect an immunologic pathogenesis before they suspect anything else. Dr. Beers' chapter – deliberately incomplete – presents blocks of non-allergic diseases which mimic allergies and should go a long way toward restoring the balance.

Treatment in allergy has followed – somewhat hesitantly – the trend of the discipline which has moved from its empirical past into its experimental present: treatment must be specific – not in an immunologic sense but in the sense of identifying the condition which it attempts to correct. Undertreatment and overtreatment – with corticosteroids, with sympathicomimetic amines – might be equally hazardous, not only in the day by day management of bronchial asthma, but more so in the control of allergic emergencies where precision alone might decide upon the outcome.

The effectiveness of immunization in IgE-mediated allergic disease has been reviewed with care by two articulate investigators: the evidence which supports the belief that it is effective has been placed into perspective by the enumeration of certain doubts which have not yet been resolved. Both authors plead for better techniques of evaluation: standardized antigens, uniform methods for the measure of antibodies, comparable skin tests, and objectivation of clinical responses. They are joined by Dr. Baer who reports on the range of potency of allergenic extracts, which is disheartening. We have made a strong move toward the improvement of standards: Drs. Spector and Farr have been given ample space for a description of the *technical* details of bronchial challenge; and we have encouraged Dr. Kopetzky to use as many pages as necessary to demonstrate clearly what pulmonary function tests can and cannot do.

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Incidence of Atopic Disease

*Jeanne Montgomery Smith, M.D.**

It is difficult to write on the incidence of atopic disease because studies reported in the literature vary in technique and terminology enough to make it hard to select those that are valid and comparable. There is a temptation to discount those findings that challenge our assumptions about the nature of respiratory allergic disease, but until we have better information, each observed difference between populations should be regarded as an avenue for further exploration. Because questions of incidence and of what sets the stage for the development of a disease are fundamental to the search for causative factors, it is important that more adequate whole population studies be made.

A very real problem in dealing with the epidemiology of asthma, allergic rhinitis, and vasomotor rhinitis with nasal polyps is whether they should be considered different manifestations of the same disease, or different diseases. If they are the same disease with host or environmental factors causing differences in clinical form, studying the epidemiology of one without the other may be like studying the epidemiology of renal tuberculosis without considering other forms of tuberculosis. Obviously, important connections would be lost. In the present state of our knowledge, it seems wisest to collect epidemiologic data in such a way that these conditions can be considered both together and separately.

Respiratory allergy is a relatively common problem in most parts of the world. By comparing studies of incidence in the United States with similar studies from other countries, differences emerge that suggest environmental as well as genetic influences. In school-aged children and young adults, there is almost no other cause for recurrent wheezing; and where seasonal hay fever is concerned, there should not be too much room for differences in interpretation. More than half the adult population with hay fever and asthma have their first symptoms before leaving school age, so that the epidemiology in childhood is relevant to that in the adult. In our own experience, half the cases of adult asthma in a general population originated in childhood but, as is also seen in other studies,

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Table 1. *Incidence of Asthma and Hay Fever in School-Aged Populations*

					ASTHMA		WHEEZING		HAY
COUNTRY AND AUTHOR	YEAR	AGE	METHOD	NUMBER	CURRENT	CUMULATIVE	CURRENT	CUMULATIVE	FEVER
New Zealand									
Milne[33]	1969	11–13	School questionnaire	952		9.2% ♂ 4.9% ♀			
Australia									
Williams and McNicol[63]		7–10	Interview and sample examined	30,000		3.7%	3.7% at 10	11.4% at 10	
Pollard et al.[36]	1971	6–11	Interview	160					
Scotland (Aberdeen)									
Dawson[10]	1969		Interview and school exam.	2,511	4.8%				
Scotland (Glasgow)									
Annual school health report[6]	1971	0–16	Interview and school exam.		.9				<1%
Finland (Rural)									
Alanko[1]	1970	10–19	Interview, exam., metacholine challenge			0.5%	1.6%		2.7%
Finland (Helsinki)									
Eriksson-Lihr[14]	1955	7–14	School questionnaire and exam.	4,832	.4% ♂ .3% ♀				
Sweden									
Kraepelein[28]	1954	5–6 14–15	School reports and interview	247,000	1.6% .87%				
England									
Morrison Smith[48, 49]	1957	5–18	Interview and exam.	49,273			1.8%	3.2%	
	1969	5–18	sample	20,958	2.3%	4.2%	5.4%	9.9%	

Switzerland									
Varonier[58]		5–6	Interview and exam.;	4,781	1.38%	1.67%		4.4%	
		15	M.D. diagnosis	2,451	.89%	1.9%			
India									
Visiomathan[61]	1966	under 10	Interview	15,805			.18%		
United States (Maryland)									
Rhyne et al.[39] elementary	1971		Interview and sample examined	3,939			2.9%	6.9%	
United States (Michigan)									
Broder et al.[4]	1962	6–8	Whole population – interviews and sample examined			4.7%		14.4%	
United States (Iowa)									
Smith and Knowler[51]	1960								
Rural		0–20	Whole population	3,249		3.0%			3.1%
Iowa City		0–20	under 20 interviewed	2,866		2.7%			3.1%
United States (Colorado)									
Freeman and Johnson[19]		14–18	Questionnaire, sample examined	2,235			2.8%		19%
United States (Texas)									
Hill[25]			School population	70,812		2.8%			
Houston Texas Schools			white			3.8%			
			Mexican-American			0.74%			
			Black			3.3%			

Table 2. *Incidence of Asthma and Hay Fever in Adult Populations*

	POPULATION	AGE	PREVALENCE OF ASTHMA (CUMULATIVE)	HAY FEVER
Vaughan, 1934[59]	Urban general populations		6.2	
Collins[8]	9,000 families			
Service,[46] 1939 (Colorado)	Urban population		3.6	10.6
Piness et al.[35] (Montana)	Urban population, company towns			4.0
Stocks,[53] 1949 (England)	Questionnaire, sample and interview	over 16		
Broder et al.,[4] 1962 (Michigan)	98,000, urban population, interview		4.1*	6.3
Smith et al.,[51] 1965 (Iowa)	Rural population, interview	over 20	4.4	6.4
Julin et al.,[27] 1967 (Sweden)	2,000 subjects, interview, exam	all	2.0	
Irnell et al.[26] (Sweden)	General population, questionnaire, interview	30–64	2.3	
Edfors-Lubs[13] (Sweden)	7,000 twins, questionnaire	47–86 by age	3.8	14.8
Alanko[1] (Finland)	Rural population, interview sample, exam	59	2.9	

*More certain diagnosis (10.2 less certain)

only a small percentage of childhood asthmatics had seriously disabling or limiting disease as adults.

Table 1 sets forth for comparison a number of studies of incidence in school children in the United States and other countries. In many reports in the literature, it was difficult to be sure whether figures referred to current prevalence or a history of attacks at any time during life. A few authors gave both figures for a "more certain" diagnosis of asthma by doctors' examination and a less certain category of history of recurrent wheezing attacks. Those who gave figures for a history of wheezing had found that skin testing and family history of atopy in such children gave the same results as in the children with the more certain diagnosis, so that it seems likely that the broader definition is actually more valid. The Finnish and Scandinavian incidence in childhood seems to be relatively low. The Geneva figure of 1.67 per cent in 5 to 6 year olds is comparable to the 1957 finding of 1.8 per cent in Birmingham, England, but is lower than recent British experience and lower than Australian and recent American reports. The highest European figures for school children are from the British Isles, with Aberdeen 4.8 per cent and Birmingham 4.0 per cent.

Table 2 shows figures for the prevalence of asthma in adults in various countries, Table 3 gives military examination prevalence rates or rejection figures, and Table 4 reports experience with university students. The military rejection data give some idea of the prevalence of asthma regarded as significantly disabling in the young adult male. Vaughan presents some interesting figures from World War I, with a recruit rejection rate of 0.25 and 1.2 per cent of veterans receiving compensation for asthma disability 15 years later. The military rates are low compared to most grade school incidence or prevalence figures. Nonetheless, asthma was the most common disabling chest condition, occurring more frequently than tuberculosis or bronchiectasis, even in the French experience where the prevalence of asthma among 190,000 18 year olds was only 0.38 per cent. University student populations usually have had an incidence of asthma and hay fever above most general population figures.

The incidence of intrinsic asthma can really only be guessed at because of troubles in defining what is meant by the term. In a rural Iowa general population study, 27 of 160 asthmatic *adults* related their attacks to infections rather than to seasons or specific inhalant exposure to animal danders or farm dusts. Of these asthmatics, 10 also had a history of nasal polyps. Since we were being careful to include as asthmatics only those people who could readily be distinguished by virtue of intermittent symptoms relieved by bronchodilators, this figure is no doubt an underestimate. It is quoted for lack of a better source of information. The relatively great importance of intrinsic asthma lies in its severity and in the frequency of disability and hospitalization. For example, in reviewing 11,551 cases in Australia, Ford[18] found intrinsic asthma in 68 per cent of hospitalized asthmatics and 44 per cent of asthmatics attending clinics.

Fewer reports of incidence for adult hay fever exist in the literature. Tables 1 and 2 give some representative figures. Most of those from other countries are much lower than hay fever incidence figures for the United States, which range from 6.4 to 24 per cent in recent studies. However, the long-term Swedish study of 7000 twin pairs has the highest rate among European reports, 14.8 per cent, which the authors regard as a probable underestimate. This reflects a cumulative prevalence over a greater number of years in an older population now aged 45 to 84 and may reflect a difference in time of onset in European patients. In the Alanko study from Finland, a gradual accumulation of incidence to almost 10 per cent emerges in the 50 to 59 age group, but in the 0 to 19 age group the incidence is only 0.5 per cent.

There has been a good deal of discussion as to whether there has been an increase in the incidence of respiratory allergy in recent years in the United States. A study of hospital admissions in Pittsburgh showed a doubling of the number and an increase in the severity of the asthma cases admitted.[17]

Another report from Los Angeles showed a great increase in the number of children hospitalized with asthma and 20 deaths from childhood asthma from 1952 to 1963 as compared with 4 from 1937 to 1953.[38] The Children's Asthma Hospital and Research Institute in Denver, Colorado (CAHRI)[15] has reported a "very dramatic change in the severity and intractability" of the asthma in patients admitted to their care. Changes in hospital admissions may reflect reduced availability of primary medical care in some communities so that it is difficult to interpret the meaning of these reports.

American mortality statistics for asthma at ages from 5 to 34 years did not show an increased death rate from asthma in the years from 1959 to 1968.[54]

Table 3. *Asthma in Populations Examined for Military Service*

	REJECTED FOR ASTHMA (PER CENT)	INCIDENCE	POPULATION
United States			
Vaughan[60]			
World War I	0.25		
Rountree[40]			
World War II	0.51 Black	0.67	45,585
	0.36 White	0.52	
Great Britain			
Williams[62]			
World War II	0.9		
Holland			
Ufford,[56] 1952			
Towns over 25,000		1.18	170,000
Towns under 25,000		0.77	
Finland			
Eriksson-Lihr,[14] 1955	0.96		2,178 (conscripts)
France			
Cotton et al.,[9] 1971	0.32	0.38	100,000 all 18 years old

In the case of the Children's Asthma Hospital and Research Institute, the increase in the severity of the disease in those admitted has been accompanied by a greater scattering of states of origin for their patients. This suggests that they are ranging more widely in taking the most severe cases from a larger number of communities, while less severe cases are possibly being managed at home with the help of newer medicines. The change in their clientele is underscored by their comment that 5 children died while their applications were being completed in 1968 to 1969 while none died waiting admission in 1958 to 1959. The kind of case admitted also has changed. A greater number of children have experienced life-threatening episodes of respiratory failure and more have had intractable asthma and aspirin sensitivity beginning after the age of 10.

One clue suggesting that the more severe intrinsic asthma may not be on the increase is a declining mortality from asthma as reported in national death statistics. However, these statistics are unreliable because fashions in diagnosis change. With the broad definition of chronic bronchitis in terms of sputum quantity that became popular in pulmonary clinic circles a few years ago, what is intrinsic asthma to some is chronic bronchitis to others.

The American asthma mortality figures for the years from 1959 to 1968 maintained an even level for patients between the ages of 5 and 34 years, but the figures for all ages decreased. This suggests that the change occurred in the age groups where most confusion of terminology exists. The mortality of the 5 to 34 year old group could reflect a continuing stable incidence, but there is no way of knowing whether better treatment might be maintaining the same mortality in spite of increased incidence.

During the years 1964 to 1969, there were reports of increased asthma mortality from Britain, Australia, New Zealand and Scandinavia which involved not only older asthmatics but children as well.[51] There was much talk of an increase in the United States and a good deal of excitement about the British discovery that the increase coincided with an increase in the sale of aerosolized bronchodilators. It turned out that the significant increase in mortality was experienced only in certain countries and seemed to be related to the sale of a particular brand of aerosol which delivered a much larger dose of isuprel than others. (This experience serves as a warning to caution patients about excessive use of aerosolized isuprel, but it is to be hoped that it will not discourage the use of this kind of medication in moderation where indicated or encourage the use of much more expensive means of delivering aerosols.) In the school children study from Birmingham, England, the 3.2 per cent incidence in 1969 represents an increase over the 1.8 per cent incidence obtained 10 years earlier by the same investigator in the same schools (see Table 1).

We do not have data that tell us without question that respiratory allergy is on the increase. The old figures and newer ones collected from many sources and summarized in Tables 2, 3, and 4 suggest that there may have been an increase. These and childhood studies suggest more strongly that certain selected populations may have much higher incidence than others, and it seems worthwhile to consider separately various factors that may influence the incidence of the disease.

Some data of our own will be mentioned from time to time.[51] These are from general population interview studies of 1760 rural families,

Table 4. *Incidence of Asthma in University Students*

	YEAR	ALLERGIC RHINITIS ONLY	ASTHMA OR ASTHMA AND ALLERGIC RHINITIS
University of Washington			
Van Arsdal and Motulsky[57]	1959	12%	4.7%
Tips[55]	1954	16.2%	7.1%
University of Wales (England)			
Grant[21]	1957	–	3.3% (1.9% active asthma)
University of Michigan			
Maternowski and Mathews[32]	1962	13.4%	5.7%
Howard University			
Sherry and Scott[47]	1968	13.9%	4%
Brown University			
Hagy and Settipane[23]	1969	19.7%	5.3%

1440 Iowa City families, and an analysis of 1106 consecutively seen clinic patients. We are situated here in the midst of the world's best agricultural land and can claim the doubtful honor of the best ragweed crop anywhere. This and a definite seasonal pattern for alternaria mold give rise to an excellent ability to recognize a high proportion of extrinsic allergies by history alone. As in all interview studies it is likely that we missed some cases, particularly among those with less serious hay fever or perennial rhinitis.

FACTORS INFLUENCING INCIDENCE

Family History

Since genetic considerations are dealt with elsewhere in this symposium, the family history will be considered here mainly from the epidemiologic point of view. The reasons for the marked tendency of these diseases to occur in families may or may not be entirely genetic, and need to be considered both apart from and within the genetic context.

The single most important factor increasing the risk of developing asthma or allergic rhinitis in youth is birth into a home where someone already suffers from these conditions. In the study of 1760 rural Iowa families, focusing on the population under 20 at the time of our interview visit, 16 per cent of the girls and 28 per cent of the boys born into allergic households had developed these diseases, as compared with 0.8 per cent of the girls and 1.5 per cent of the boys born into households without allergic members. An analysis of our allergy clinic population showed 87 per cent of our patients under the age of 10 had a positive family history and 80 per cent had affected relatives living in their homes. These figures for family history are high in comparison with some other reports in other environments. We are in a locality with exceedingly high exposure to alternaria mold and to ragweed which may increase the ease with which the disease is recognized by history in relatives. (On the other hand, environmental influences might reduce the number of cases occurring outside affected families.)

The mother seems to be an important factor in the development of asthma. A carefully planned epidemiologic study of asthma in children in this country is being made by M. Britt Rhyne in Baltimore.[39] She has found that the influence of the presence of the disease in the mother outweighs other factors, and only where the mother is not affected are other environmental influences statistically associated with differences in the incidence of asthma. In our own studies, the Mennonite or Amish population showed an interesting difference from the remainder of the population in that the small child with asthma was twice as likely to have an affected mother as an affected father. In the rest of the communities we studied and in most figures from literature, there is a slight but usually statistically insignificant difference in the number of allergic children with affected mothers as compared with affected fathers. Exceptions are old figures from Bray[3] in England and Schwartz[45] in Denmark who found mothers affected twice as often as fathers. Schwartz

Table 5. *Comparison of Closest Relative Affected in the Clinic and in Rural Populations*[*]

AGE	MOTHER		FATHER		BOTH		GRANDMOTHER		GRANDFATHER		AUNT		UNCLE		SIBLINGS ONLY	
(Years)	Clinic	Rural	Clinic	Rural	Clinic	Rural	Clinic	Rural	Clinic	Rural	Clinic	Rural	Clinic	Rural	Clinic	Rural
0–9	78	75	58	57	11	16	19	10	10	10	14	18	15	18	20	32
10–19	16	14	8	14	2	14	5	2	2	1	5	1	3	6	13	7
20–29	6	6	13	11	1	3	2	3	1	1	2	1	2	4	14	12
30–39	6	2	2	0	3	0	1	2	2	0	2	1	2	0	12	7
40–49	2	2	6	2	3	1	0	1	0	0	0	0	1	0	4	4
50–59	4	0	4	1	0	0	1	0	0	2	0	0	0	0	6	1
60–69	2	0	2	0	0	0	0	0	0	0	0	0	0	0	0	0
No age given	0	4	1	0	0	0	0	0	0	0	0	0	0	0	2	7
Total	114	103	94	85	20	34	28	18	15	14	23	21	23	28	71	70

[*] Including the siblings *only* group, there were 398 with a positive family history of a total of 611 in the clinic study and 373 of 603 in the rural study.

explains this finding on the basis of unreliability of the data on men. Recently Ryan also has found more affected mothers and comes to the conclusion, with some justification, that since the data are almost always collected from mothers, the information about fathers is unreliable. Since more males have asthma and hay fever than females, fathers should be affected more often than mothers. It is possible that environmental factors increase the importance of the mother in some social settings, and a better attempt to get reliable information about fathers should not be dismissed without further careful study.

Table 5 gives our own experience with family history in our general population rural and city studies. It can be seen here that the father seems to be slightly behind the mother. One could suppose that the data on fathers might be a little less reliable except that the heavy occupational exposure in the farm group ought to make most cases quite obvious.

In intrinsic asthma, various authors have found the incidence of a positive family history of allergic rhinitis or asthma greater than for a general population. In our own experience of 140 patients with nasal polyps and intrinsic asthma, 58 per cent had a positive family history as compared with 34 per cent of the general population. Samter[43] reports 65 per cent with positive family history or affected children among 164 patients with aspirin sensitivity, intrinsic asthma, and nasal polyps.

In spite of the clear importance of the family history in the risk of developing respiratory allergy, a study of 7000 twin pairs from Sweden shows that although monozygotic twins are more often both affected than dizygotic twins, the difference is small and both twins are affected less than half of the time. They note that "the environmental factor is of great importance also in developing asthma, hay fever, and eczema."

In our original clinic study we had become interested in the possibility that some factor (perhaps infectious) requiring close contact might have a role in the development of the asthma–hay fever group of conditions. We began by asking our patients whether they had ever lived with anyone with these diseases and discovered what seemed to be an increased risk for those married to an affected partner. In the clinic study, 20 per cent of patients developing asthma or hay fever as adults without a family history of the disease had done so after marriage to an affected partner, as compared with 7 per cent of a control population married to normal spouses. The findings in the rural population and in a city population were essentially the same as the clinic experience, with asthma or hay fever developing in 20 and 30 per cent after marriage to an affected partner. These figures are significantly different from the control population experience gathered by us, but as can be seen from many other studies, the figures for the general population incidence in this country run all the way from 7 to 24 per cent, and we are faced with the problem of the reliability of interview data.

Age

Youth is a strong predisposing factor for the development of both hay fever and asthma in those born into allergic families. For those born into allergic households, the risk is extremely high in the first few years of

Table 6. *Relationship of Age at Onset of Symptoms to Markedly Positive Skin Tests**

ONSET	UNDER 10	UNDER 20	UNDER 30	OVER 30
	58%	79%	92%	8%

*From an analysis of 1106 clinic patients using 18 common inhalants

life, falls sharply to the tenth year, and falls somewhat less sharply to the twentieth year. Thereafter the risk of developing first symptoms in the mid-twenties becomes quite low but remains slightly higher for young women born into allergic households than for young women not born into allergic households.

Youth is also an important factor in determining the incidence of severe or multiple sensitivity. Tables 6 and 7 show our experience with 1106 clinic patients with regard to the age at onset of symptoms in those with marked skin reactions or several sensitivities. Whatever sets the stage for sensitization appears to be much more likely to affect several responses or several gamma E forming clones in youth than later on. (These observations should be of some practical importance in advising young allergic parents that the very high risk for sensitization in their children is in early life and that this time before allergy develops is the time to keep exposure to unnecessary allergens like indoor pets, feather pillows, and old overstuffed furniture to a minimum.)

Concerning the age of onset in asthmatic clinic patients, some figures from various authors and our own experience are as follows: Ford[18] found an onset under 15 in 40 per cent and under 30 in 67 per cent of 11,551 asthmatics in hospitals and clinics in Australia. Derrik[11] in Sweden found that 72 per cent of 354 males and 55 per cent of 407 females had their first attack under 10 years of age. Among 876 Iowa clinic patients with asthma, 61 per cent had developed asthma before the age of 20, and of 330 who had allergic rhinitis, 38 per cent had developed it under 20 years of age.

In the Iowa general rural population 76 per cent of patients with asthma and 61 per cent of patients with allergic rhinitis had become symptomatic before 20 years of age. Table 8 shows some figures from the Iowa rural study with regard to the age at onset and sex incidence of hay fever and seasonal asthma in the adult with continuing symptoms. The experience shown here is similar to that in many other studies, with boys affected more frequently than girls in the first decade, more new cases of hay fever in girls during their teens, and the men catching up and passing the women by a small margin after age 30.

While youth is a strong predisposing factor in the development of allergy, it is evident that allergy can occur at any age. Ford, in the previously mentioned analysis of 11,551 asthma patients, found 12 per cent of those beginning symptoms after 60 years of age allergic to extrinsic factors.

Intrinsic asthma (defined as the form of asthma usually without demonstrable allergy but with hypertrophic sinus disease or nasal polyps

Table 7. *Relationship of Age at Onset of Symptoms to Three or more Positive Tests**

ONSET	UNDER 10	UNDER 20	UNDER 30	OVER 30
	75%	90%	99%	1%

*From an analysis of 1106 clinic patients using 18 common inhalants

and a tendency to mucus plugging) is far more likely to occur for the first time in adult life and at least 80 per cent of patients with this form of disease begin their disease beyond 20 years of age. This kind of asthma or hypertrophic rhinitis with nasal polyps can occur at any age but very fortunately is uncommon in childhood. Even in childhood, intrinsic asthma (as defined above) is more likely to develop after 10 years of age than before. In our experience with analysis of 1106 consecutive patients with asthma, allergic rhinitis or nasal polyps, there were 11 patients with nasal polyps and asthma among 398 patients under the age of 20. Among the 140 patients of all ages with nasal polyps, 9 per cent had developed symptoms under the age of 10, another 9 per cent between 10 and 20 years of age, and the remaining 82 per cent had developed symptoms as adults. Since ours is a referral allergy clinic, we see a selected population with more severe disease and the figures for polyposis will presumably be higher than in a general population of people with perennial rhinitis.

Sex

The great majority of studies show a two to one male to female ratio of incidence of asthma under the age of 10, with some catching up by females during their teens and middle life, after which males again show an incidence above, though only slightly above, females. Curious exceptions suggest that environmental factors may influence the sex ratio. For example, in Geneva school children, the boy/girl ratio was reported as 4/1, while the boy/girl ratio in the Maryland school children from large

Table 8. *Sex and Age at Onset of Hay Fever and Seasonal Asthma in a Rural Iowa Adult Population*

AGE AT ONSET	NUMBER	PER CENT OF TOTAL	MALE	MALES WITH SEASONAL ASTHMA	FEMALE	FEMALES WITH SEASONAL ASTHMA
0–9	99	38	60	25	39	17
10–19	48	18	17	4	31	4
20–29	47	18	23	6	24	2
30–39	35	13	23	3	12	5
40–49	21	8	10	6	11	2
50–59	8	3	2	1	6	1
60+	4	2	2	1	2	2
Total	262	100%	137	46	125	33

Catholic families and in our Iowa Amish children was 1/1, in contrast to other groups in the same rural area with the usual 2/1 ratio.

For hay fever there are fewer sex incidence figures in the literature. Table 8 gives some sex incidence figures for seasonal asthma and hay fever from our own experience with a rural population.

Intrinsic asthma as seen in various hospital patient populations seems to have a distinct predilection for the female; however, the disease may be more often confused with chronic bronchitis or emphysema in the male smoker. It is important to realize that young women of childbearing age may have very severe life-threatening intrinsic asthma. Because of their youth, there is a temptation to try to do without or to discontinue steroids prematurely. This special group of high risk asthmatics should be appreciated and treated with caution.

Allergen Exposure

How often does allergy fail to develop for lack of exposure to a suitable allergen during the time when whatever sets the stage for sensitization is active? And how often does existing allergy fail to show itself for lack of recurrent exposure to allergens? These are good questions that are not readily answered.

The much greater incidence of hay fever in the United States as compared with Europe suggests that ragweed may make a real difference in incidence (Tables 1 and 2). On the other hand, the incidence of hay fever in the Swedish study of 7000 twins reaches 14.8 per cent. These twins have been followed over a much longer period than other European populations studied, and the high cumulative prevalence suggests that the presence of ragweed perhaps may affect an early onset of symptoms more than the eventual incidence of hay fever.

Exposure to molds and pollens in farm occupations is undoubtedly much higher, and symptoms are more troublesome here than in the urban environment. However, in several studies the frequency of sensitization seems to be highest in suburbia, slightly lower in midtown, and lowest on the farm.

In the French military service examinations report, it is remarked that rural boys have asthma less frequently, but figures are not given. The Dutch military also found fewer young men unfit by reason of asthma in communities of less than 25,000 than in larger communities. In our Iowa population studies we found asthma in every fourth household in Iowa City (population 50,000), and in one of every five in the nearby rural area. In Maryland, Rhyne skin tested asthmatic children with ragweed, grass, and dust. Ragweed gave positive tests in 15.3 per cent of urban, 21 per cent of suburban, and 8.3 per cent of rural children. Grass tests were positive in 17 per cent of urban, 10.2 per cent of suburban, and 6.7 per cent of rural children. Although urban children had more positive tests for dust than rural and suburban children, the difference was not significant. There is a little evidence to suggest that animals living in the household increase the incidence of asthma as well as the chance of sensitization to a specific animal. Rhyne found that the presence of a dog when a boy was under 6 years of age was statistically significant to an increase in the incidence of a history of asthma (except as mentioned before, where the mother was affected, all other environmental factors were outweighed in Rhyne's experience).

Although both the general population studies and clinic patient experience in Iowa show higher rates for positive family history in atopic allergy than many studies elsewhere, the high level of allergen exposure may improve recognition of the disease in relatives. It should also improve the recognition of the disease in the general population, but the total population reporting allergy in the Iowa rural study was 9.9 per cent, which is not as high as that reported for many urban studies where exposure to ragweed and alternaria is much lower. From this experience and that of the various other authors reporting rural urban comparisons, it seems certain that allergen exposure is only one of the factors influencing the incidence of respiratory allergy.

Race

Morrison Smith in England reports some interesting figures from studies of school children with regard to possible interplay of environmental factors and race (Table 9). It can be seen that though there are statistically significant differences between racial groups, the differences seem to diminish as environmental differences diminish. In this country, studies of Maryland children by Rhyne show no statistically significant difference in the incidence of asthma among Negroes as compared to whites. Black students at Howard University in studies by Sherry and Scott show an incidence of 4 per cent for asthma and 13.9 per cent for hay fever which is about the same as other modern college figures shown in Table 4.

In a study of 70,912 school children in the American southwest in Houston Public Schools, Hill found an incidence of asthma of 3.8 per cent in white children and 3.3 per cent in Negro children and in only 0.74 per cent of Mexican-American children. (In this paper there is no note about how the questionnaire was administered "through the school nurse.")

No general incidence studies for Orientals could be found, but 75 im-

Table 9. *Race and Country of Birth in Birmingham (England) School Children with Asthma*

	ASTHMA	RECENT ASTHMA	WHEEZE	RECENT WHEEZE
European				
Born in United Kingdom (19033)	4.3%	2.3%	5.8%	3.2%
Negro				
Born in United Kingdom (689)	6.8%	5.5%	10.4%	6.1%
Born outside United Kingdom (273)	1.1%	0.4%	2.9%	1.1%
Asian				
Born in United Kingdom (173)	1.1%	1.1%	4.0%	2.3%
Born in Asia (296)	1.7%	1.7%	3.7%	1.7%
Born in Kenya (77)	5.2%	5.2%	6.5%	2.6%

Table 10. *Skin Test Reactions According to Social Status*

SOCAL CLASS	RAGWEED	GRASS	DUST
High-medium	19.7	18.2	22.7
Low	12.7	7.8	10.7
Low-low	7.9	3.2	6.3
	$P < .05$	$P < .02$	$P < .02$

migrant Chinese students in the Maternowski and Mathews[32] studies at Michigan had a 16 per cent incidence of ragweed hay fever or asthma, and 41 students from the Near East had a 12 per cent incidence. From India, Viswanathan et al.[61] give an asthma prevalence figure of 1.94 per cent for males and 1.54 per cent for females based on an interview study of 15,805 persons.

In view of Morrison Smith's experiences with various races in his school study it is not clear what differences in racial incidence can be attributed to race and which to environment.

Social Class

In several studies populations are separated into upper income, middle income, and low income groups. In all, the incidence of asthma and hay fever increases with increasing wealth. This might explain the repeated finding of higher rates in university student populations. Rhyne divides the group of children in her study tested with dust, grass, and ragweed by social class with the interesting differences shown in Table 10.

The reactivity rates were highest in upper social class for all aeroallergens and the differences are highly significant for grass and house dust.

The clearly lower incidence of sensitization in the low-low income group suggests that social factors offer protection (perhaps somewhat as environmental and immunologic factors combine to reduce the incidence of paralytic poliomyelitis in poorer populations).

Mobility

There is some evidence that the mobility of populations may influence the incidence of asthma and allergic rhinitis. A very old study by Piness and Miller[35] of a new company town formed around an industry, and immigrant studies by Maternowski and Mathews[32] show an increase in new cases of asthma and allergic rhinitis during the first few years after settling in the new place. For example, new cases of ragweed pollen sensitivity were more than 10 times more common in immigrants than in native students. It is of some interest that in these situations, the majority of new pollen-sensitive patients have not had previous experience with other respiratory allergy in their country of origin. Most of them seem to be genuinely new cases and have a much lower rate of positive family history than most other patients developing extrinsic allergy (33 to 36 per cent as compared with 62 to 64 per cent of native students in Mathews' study).

Rhyne finds that there is a statistically significant relationship between the number of address changes and the incidence of asthma in certain groups of children but not others.

Whether this influence of mobility is caused by exposure to different allergens, stress, or some other factor, it might well explain some of the changes in incidence and different experiences of various populations.

Pollution

There is abundant evidence that air pollution increases the activity of existing asthma. The effect of pollution on the development of new cases is decidedly less clear. Among military men developing asthma when stationed in Tokyo and Yokohama, an area of high pollution, some patients had blood and sputum eosinophilia and others had chronic obstructive pulmonary disease that was less certainly asthmatic and associated with heavy smoking. Maternowski's and Mathews' experience of a high incidence of new cases of respiratory allergy in immigrants could have its counterpart in such a service situation, with the function of pollution being that of providing new allergens and irritants to make the disease active. In any case, this Tokyo-Yokohama experience is one of the few in which pollution seems to have been associated with the development of new cases of asthma.

In studies by Rhyne in Baltimore, Maryland, the less affluent and more polluted districts had fewer asthmatic children than the less polluted suburbs. In a Japanese study[20] of school children living in Kitokysuku, a two-fold increase in asthma was noted among children living in polluted districts (10.2 vs. 5.5). In another Japanese study, Fugi City was divided into sections of high, medium, and low pollution and the school children studied for morbidity from asthma. The morbidity rate was given as 2.4 per cent for sections of high pollution, 1.5 per cent in sections of medium pollution, and 0.88 per cent in sections of low pollution. Studies following the patterns of asthma clinic visits have been made and related to pollution, to changes in temperature and barometric pressure, and sometimes to allergens. Booth[2] and his colleagues made a study of hospitals in 7 cities and found the experience of a late fall peak in asthma visits common to all. Here in a rural area of Iowa with no industrial pollution, we have the same late fall experience, usually with children and young adults sensitive to alternaria mold. Rightly or wrongly, we have attributed the problem to fall season respiratory infections in this particular allergic population.

Epidemiologic studies of the frequency of asthmatic attacks or clinic visits comparing one area or one community with another of necessity must take into account the number of asthmatics at risk for exacerbation by a nonspecific factor such as pollution. Seasonal asthmatics who have no trouble outside a specific season may not react with appreciable asthma on exposure to pollutants out of their season, and those with intrinsic asthma may be very readily upset at any season. The many variables make it very difficult to compare districts or populations with regard to the effect of pollution on asthma morbidity.

Infection

The onset of asthma is quite frequently associated with what appears to be an acute bronchial infection. Although we see this in practice and find this statement in textbooks, the only figures that could be found describing the actual incidence of this phenomenon were those of Pearson[31] in England who studied the natural course of asthma in 625 patients. "Of 393 patients who attributed their first attack of asthma to a specific cause, 103 stated that it followed an attack of bronchitis, 12 measles, 15 whooping cough, and 54 pneumonia or other nonspecific respiratory infection." It is generally thought that these infections simply "bring out" a tendency to asthma that was awaiting such a trauma to show itself and this may be the case. On the other hand, Falliers and his colleagues[25] have studied two pairs of identical twins, one of each pair having severe asthma, requiring admission to their residential asthma treatment center, and the other having mild allergic rhinitis. At the onset in both instances, the child with asthma had experienced a bronchial infection not experienced by the child with only nasal symptoms. In these cases, there is a strong suspicion that an environmental factor influencing the incidence of asthma is an infection of some kind. This study is particularly interesting in that the twins were carefully studied for parameters such as skin sensitivity and IgE levels as well as for sensitivity to metacholine inhalation and for leukocyte adenylcyclase function. The twins showed comparable wheal and erythema skin reactions but not identical allergen specificities. The asthmatic members were sensitive to metacholine inhalation and showed a decreased leukocyte adenylcyclase response, while the nonasthmatic twins did not show these abnormalities.

The relationship of respiratory infections to exacerbations of asthma has been repeatedly observed and certain viruses such as parainfluenza and respiratory syncytial virus (both syncytia-forming viruses) have been reported to cause more severe exacerbations than others.[31] Much more information is needed to assess the role of infections as possible determining factors in the incidence of either nasal or bronchial respiratory allergy.

Incidence of Asthma in Patients with Hay Fever

There has been a good deal of controversy about the frequency with which patients with hay fever can be expected to develop asthma. Whole population studies should give the best indication of significant asthma developing in hay fever patients. Broder and Mathews'[4] studies in Michigan suggest a figure between 5 and 10 per cent, and Freeman and Johnson[19] in Colorado report that only 3.4 per cent of 528 asthmatic teenagers gave a history of hay fever for more than 1 year before the onset of asthma.

Incidence of New Allergy in the Already Allergic Patient

It is not generally appreciated that whatever sets the stage for atopic sensitization repeats itself only occasionally in the course of life. As a general rule, beyond a period in early childhood, once we see the patient who has developed positive skin tests to various allergens, the pattern we find is the one that will remain for many years and only occasionally will a new *unrelated* allergy appear. We do not even know with certainty how long the easily sensitizable state remains. For example, we assume that it lasts at least several months, because we see spring and fall hay fever in the same person, but there are fall pollinating varieties of several trees and many grasses. Better data are needed before conclusions are drawn about the nature or duration of the events surrounding sensitization. Deliberate attempts to sensitize atopic and normal people have been made by a number of investigators.[22, 30, 41, 44] With a few exceptions, the response of atopic patients to injections of vaccines and allergens has not been detectably different from normal. The few exceptions could be explained on the basis of prior immunologic experience with any of the allergens that have so far been used. Allergens sprayed into the nose give some different responses among atopics, but it is still not clear whether these are true long-lasting symptomatic responses similar to the spontaneous disease rather than differences induced by abnormal membranes.[27, 51]

In the many follow-up studies in the literature, there seems to be little mention of the development of new allergy. Rachman,[47] in his follow-up of 688 children after an interval of 20 years, found 114 primarily with dander sensitivity. Among these, 17 later developed hay fever, but only 2 did not have positive pollen tests at the original visit.

In our own recent follow-up study of 245 students with allergy tested 15 to 25 years earlier, 13 alumni thought that new allergies had developed, but in 5 of these, related allergies to trees or grasses were already known to use from their original tests.[50] It is well known and recently more clearly documented again by Hagy and Settipane[24] that skin tests may be positive several years before symptoms occur.

In our search for the factors that set the stage for or determine the incidence of atopy, the frequency of repeated sensitization is important. Better information than any we now have is needed to clarify the place of the sensitization phenomenon in the total picture of asthma and its nasal equivalents.

Incidence of Penicillin Reactions in Patients with History of Penicillin Sensitivity and in Patients with Atopy

The incidence of penicillin reactions in people with a history of previous reaction has been reported by various authors, particularly in relation to efforts at skin testing for the prediction of systemic reaction. A good example of these experiences is that of Brown[5] who tested with penicilloyl polylysine (PPL), a protein-penicillin conjugate, 1003 patients with a history of penicillin reaction; 39.5 per cent had positive skin tests with either or both of these test materials. Among 13,489 patients without a history of reaction to penicillin 6.5 per cent had positive skin tests. Systemic reactions occurred in 4.2 per cent of 212 patients with 2+ PPL and in 10.2 per cent of 206 patients with 4+ PPL tests. Reactions occurred in 0.5 per cent of patients with a history of penicillin sensitivity but negative skin tests. Other minor determinants are presumably the cause of these reactions.

Because of the expectation that atopic patients will be readily sensitized to penicillin, this drug is often avoided in patients with asthma or hay fever. Actually the incidence of atopy among patients with penicillin reactions is only slightly greater than in a general population. A recent study of 1043 subjects entering a health maintenance organization plan showed skin tests positive to penicillin haptens in 3.9 per cent of people with hay fever or asthma and 4.4 per cent of subjects with no history of atopy.[52] However, de Weck believes that "it has been convincingly established, for penicillin at least, that patients with an atopic constitution are also predisposed to develop immediate type of hypersensitivity to drugs."[12]

Incidence of Urticaria in Atopic Patients and the General Population

A number of studies give figures for incidence of a history of urticaria. The numbers reported vary from 3.2 to 12.8 per cent of the population. The incidence of a history of urticaria in patients with asthma or hay fever varies from 2.9 to 14.4 per cent in the various reports, and Schwartz, who made a statistical analysis of the incidence of urticaria in families of asthmatics, came to the conclusion that a history of urticaria was not more frequent in the relatives of asthmatics than in the relatives of his control population. On the other hand, in the 7000 twin pair study there was a small but significant association of urticaria with respiratory allergy in individual subjects.

Recently Lars[29] reports from Sweden on the incidence in a total general population of 36,475 physically examined for urticaria. The prevalence was 0.11 per cent among males and 0.14 per cent among females. Thirty-one per cent of the cases in males and 34 per cent of the cases in females were acute rather than chronic.

Incidence of Food Allergy in the Atopic Population

There are no reliable data on the incidence of food allergy in the atopic population. If consideration is given only to those conditions that are epidemiologically associated with atopy, asthma, allergic rhinitis, atopic eczema, and vasomotor rhinitis with hypertrophy, the incidence of provable food allergy is quite small. There are no incidence figures from general population studies, and clinic figures rarely give the criteria on which the diagnosis was made.

The statement that food allergy is more common in childhood is repeatedly made in the literature. From the description of cases it seems likely that this statement has a basis in fact, but actual numerical data with stated criteria are lacking. Acute asthmatic reactions to such things as nuts, shellfish, or egg happen in fewer than 1 per cent of clinic patients in our experience. Less definite reactions are much harder to prove and, though they exist, no meaningful figure can be given.

Other symptoms attributed to food allergy, such as the tension-fatigue syndrome or headache, are not atopic as far as we know, and the existence of such syndromes related to food are open to question. It is possible that some symptoms attributed to food allergy may have to do with the effects of dietary change on bowel flora or metabolic needs. Although it is legitimate to experiment with foods in the hope of giving relief, such individual experimentation should be done without giving allergy as the necessary explanation and with full realization that it is not hard to mislead either the patient or ourselves in the very difficult area of food trials. There seems to be no point in quoting incidence figures for food allergies when both the allergic nature of the symptoms and the means for their diagnosis such as oral challenge with food extracts are open to serious doubt.

SUMMARY

In spite of difficulties with methods and the limitations of survey techniques, the available evidence makes it likely that the reported differences in incidence from country to country and within local populations are real. It is an assumption that allergy is the *cause* of these diseases: although pollens are an important factor particularly in seasonal allergy, it is evident that allergens are not the only factors at work in deciding the incidence of asthma and probably hay fever. Since natural history and epidemiology of a disease give direction in searching for causes, more carefully planned studies are much needed.

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Genetic Aspects of Allergy

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Among the predisposing and contributory factors in allergy, heredity is almost universally included; it is presumed to play a major role in the establishment of the allergic state. The tendency to allergy is clearly familial, although the specific clinical reaction is not directly inherited.

The familial nature of the allergic diseases is apparent: one is more likely to find an allergic individual with an affected relative than to find an allergic individual in a family that is unaffected by allergy. Indeed, the term *atopy* has come to mean that the hypersensitivity is characterized by a familial tendency. Since the total of man's response is ultimately dictated by the interaction of his genes with his environment, the incidence of allergy can be changed only by breeding selectively for nonresponsive individuals in that environment or by altering the environment.

There are two reasons for studying heredity in allergic diseases. Of most direct importance to the clinician is the need to supply to a patient or the family of a patient the counseling that provides empirical risk data for allergy appearing in subsequent children. The inquiry frequently comes from couples who have a severely affected child and who want to know the chances of recurrence if they were to have another child. Couples who are contemplating marriage or who are married but have not yet had a child are often concerned about the risk of having a child with severe allergy if one or both of them have had uncomfortable lives because of their allergies. The need to know the risk is important to some people for family planning.

Knowledge of the nature of inheritance may also be used as evidence for the mechanism leading to allergy. At present, such information is of little practical value to the clinician; in time, however, it may influence the direction of research.

The discussion of the role of heredity in disease often fails to clarify the significance of the term *genetic basis* of the disease state. The term *familial disease* is well understood; it means that the disease appears to run in a family. This occurrence in a family may be simply a result of

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common exposure to an environmental condition that is totally responsible for the disease state; for instance, silicosis in a family of quarrymen or tuberculosis in a family living in close quarters with an active case in their midst. On the other hand, the familial tendency may result from the inheritance in a simple Mendelian fashion of a gene that is wholly responsible for the disease; for example, Tay-Sachs disease, cystic fibrosis, or Duchenne muscular dystrophy. Another set of genetic diseases are due to chromosomal aberrations which may be familial, such as chromosomal translocation in Down's syndrome. In these last two sets of examples, the disease will become manifest regardless of environmental conditions.

Although there have been several reports over the past 50 years that certain allergic diseases are inherited as simple Mendelian dominant or as simple Mendelian recessive characteristics, the general consensus is that "familial incidence" implies genetic systems involving more than one gene and involving, as well, some environmental component. Such inheritance is called multiple factor inheritance. Several reviews have been written delineating the various genetic theories and their supporters. For anyone who is anxious to find support for his particular point of view, the papers by Edfors-Lubs,[4] Schwartz,[11] Leigh and Mallory,[6] and Ratner and Silberman[13] are pertinent.

The purposes of this article are to clarify the meaning of the terms "inherited" or familial tendency and to describe the methods used to arrive at certain conclusions about the genetic component in allergic manifestations. Further, the evidence for the genetic basis of some of the component systems in the immune response will be examined to show that the great variability that exists between individuals who are allergic might have some basis in inherited differences in the immune response.

If allergy has a major genetic component, certain implications must be understood. What is inherited is not a trait, but rather a gene, which is the coded information for a sequence of amino acids called the primary polypeptide. The polypeptide, as the product of the gene, participates in the complex of pathways leading to a final trait. Thus, one does not inherit a disease from a parent; one inherits only the information coding for a polypeptide that in a particular environment results in unusual responses. The ultimate expression of the gene can be modified by the presence of other genes or by variations in the total environment.

The environmental component in allergy is of major import. Nonexposure to an allergen may account for the difference between lack of symptoms and presence of symptoms. The lack of challenge of the environment to a genome (the total array of genes in an individual) may lead to regional differences in frequency of allergic diseases. One must, on the other hand, exclude abnormal distribution of genes in the population before concluding that regional difference in allergens is the basis for regional disease frequency differences.

Genes are simply the basic units of genetic information. The recognizable carrier of genetic information in the cell is the *chromosome*. Except for the sex chromosomes in males, all chromosomes are paired; the exact number of chromosomes in man is 46 or 22 pairs of autosomes and 2 sex chromosomes.

The site on the chromosome that is occupied by a gene is called the *locus* and is relatively permanent. Different forms of the gene at the same locus are called *alleles*. The alleles are basically a family of genes which have almost the same DNA structure and which control a specific end product or function. Examples of alleles are the three blood group genes – A, B, and O – and the two hemoglobin genes – A and S.

Since the chromosomes exist in pairs, each cell has two editions of each gene; and depending on what each of the parents has transmitted, the two genes may be alike or different in their structure and their product. If both alleles are alike, the individual is called *homozygous* for the trait; if the alleles are different, he is termed *heterozygous* for the trait. If there are in the population only two alleles at a particular locus (e.g., *X* and Y), there can be two kinds of homozygotes (*XX* or *YY*), but only one kind of heterozygote (*XY*) for the trait.

The action of the gene – that is, the interaction of one allele with another allele in an individual – gives rise to the terms *dominant* and *recessive*. If the presence of one allele is sufficient for the manifestation of the trait, this allele is called a dominant gene. Thus, a heterozygote for the mutant gene for Huntington's chorea will have the disease since the mutant gene is dominant. A gene is called recessive if a trait is manifested only when two copies of the same allele are present.

Although we imply that a gene or pair of genes is responsible for a trait, the complexity of man's biochemistry suggests that no gene functions independently of other gene loci and of the environment. Because of the great variability among individual genomes, there are some gene-controlled traits which are not manifest in all persons. The terms used to describe the variability in trait manifestation are *penetrance* and *expressivity*. For example, a gene may be dominant and present, but only 60 per cent of the individuals with this gene show evidence of the gene's action. This allele would be said to be 60 per cent penetrant. The allele may not be expressed in a parent, but it may be expressed in a child who has received the gene from an unexpressed parent. Some theories on the inheritance of allergy rely on the concept of variable penetrance.

To understand simple Mendelian inheritance, we must also consider the origin and significance of an allelic series of genes. We may assume that in the beginning there is only one allele – the normal gene. The second allele arises as a mutation occurs, mutation being a stable change in the genetic information which occurs within the locus. The mutation leads to a slight change in the amino acids making up the primary polypeptide, and this slight change may result in a major change in function or manifestation. The two alleles now existing in the population, either as homozygotes or in a heterozygous combination, result in identifiable contrasting characteristics.

Practically all characteristics, both normal and pathological, which are considered genetic fall into one of three categories which affect the state of development, function, or reaction. These basic mechanisms are as follows: (1) chromosomal aberrations, (2) mutated genes at one locus, and (3) multiple factors involving more than one locus. In all situations, the environment may be an additional, major consideration.

Chromosomal aberration implies that the normal number of chromosomes (46 in man) or that the normal amount of chromosomal material is not present; and, as a result, a major impact is made on total development. For example, in Down's, or Turner's, or Klinefelter's syndrome, a number of anomalies are found – usually including mental retardation. The term syndrome is commonly used for the state resulting from chromosomal abnormality because a number of different developmental systems are disturbed by the presence of quantitatively different genetic information. For discussions of allergy, we can quickly dismiss chromosomal aberrations as a causative factor.

Most of the theories on the inheritance of allergy or the allergic tendency fit into either the single mutant gene category or the multiple factors category.

The single mutant gene theories are those which state quite simply that allergy is inherited as a Mendelian recessive gene or Mendelian dominant gene. What is implied is that at the locus involved in allergy there exist at least two alleles in the population; and since every individual must have a pair of genes controlling each trait, any one individual may inherit from his parents two similar genes or two different genes for a trait. The combination obtained is responsible for susceptibility to allergy. Thus, all that a parent transmits is the gene for allergic tendency and not the allergy *per se*.

The recessive theories fall into two categories. The most commonly held theory is that the homozygous recessive has the tendency for allergy, but the specific allergen(s) to which he becomes sensitized and the manifestation of the response are dictated primarily by the environment. A variant on this theory, proposed by Wiener et al.,[18] implies that the homozygous recessive individual has 100 per cent penetrance and manifests symptoms before puberty. The heterozygote has variable penetrance and therefore may or may not have symptoms of allergy. The remaining homozygous genotype leads to a normal individual with no allergy potential.

A second set of theories involving recessive genes is based on the idea that individual loci are responsible for each individual type of hypersensitivity. Thus, allergic rhinitis or bronchial asthma is the product of the action of a specific locus. An individual may have more than one form of allergy if he has received from his parents two recessive genes at each of two or more of the hypersensitivity loci.

In addition to the theories that hold allergy to be a product of recessive genes, a number of theories have presumed dominant gene inheritance of the allergic state. According to these theories, an allergy gene, even in a single dose, can lead to susceptibility to allergy. Here again, some believe that only one locus is responsible for all allergy, as opposed to others who feel that each form of allergy represents a separate locus.

All the theories so far mentioned include, of necessity, the possibility of variation in expression of the inherited gene. Thus, the homozygous recessive may not show allergy even in an environment where sufficient allergenic stimuli exist. In the many published estimates on penetrance in allergic diseases, the range of penetrance has been calculated to be between 40 and 100 per cent.

The final general class of inheritance includes a large variety of normal traits such as height, weight, and intelligence, as well as disease traits such as schizophrenia, diabetes mellitus, and hypertension. This form of inheritance, called multiple factor or polygenic inheritance, is dependent on the interaction of genes from more than one locus; each parent may, therefore, contribute several genes to make up the individual's constellation of genes affecting allergy. In general, the pattern of inheritance of polygenic traits does not resemble the simple regular patterns seen in the pedigrees characteristic of single gene effects; the deviation from a regular pattern and obvious concentrations in some families account for the use of the term *familial disposition*. The many genes that play a role in the characteristics under discussion are inherited as alleles at several loci, but there may be an additive effect of the various dominant or recessive genes, as well as an effect of the environment, on the final configuration we classify as allergic or not allergic. Because we cannot identify individual loci in polygenic inheritance, we do not have to rely on the concept of expressivity involving any single gene.

In diseases that are inherited as multifactorial, an additive series of genetic factors is presumed; this, together with the environment, determine the liability of an individual to develop allergic manifestations. The additive effect implies a "threshold," above which the recognizable disease develops. The threshold concept provides a graded scale of liability and can account for the variation among siblings or among parents and children in the manifestation of allergy without the necessity of postulating variation in expression of a single gene or single locus.

With a hypothesis of multifactorial inheritance, we rely on empirical risk data in dealing with the probability of allergy occurring in children; that is, we use collected data based on incidence of the allergy among first degree relatives for our estimate rather than on the probabilities inherent in single gene transmission corrected for degree of penetrance.

Inherited traits may be considered continuous (metric) traits or discontinuous traits. In either case, each trait must be identified or quantified and then classified. Errors or variations in classification may lead to the inability to generalize or to prove or disprove a genetic hypothesis and can account for discrepancies between different data collections. Failure to classify uniformly is but one source of difficulty in drawing and testing genetic hypotheses relating to allergy.

Another source of difficulty is sampling. Quite often we see published data on the frequency of allergy in a population based on the findings of clinical allergists. In these studies, families who have no history of allergy are generally excluded. Such a sampling bias yields a much higher frequency of allergy than is actually present. This is called the bias of ascertainment; that is, it is based on populations determined from affected individuals, and it will yield false conclusions – the tendency being to overestimate the ratio of affected to normal offspring in families. With a single recessive gene hypothesis, this type of family study, although dependent on family size, would appear to result in a 1:1 ratio of normal to affected rather than the 3:1 ratio expected when both parents are heterozygotes for the recessive trait.

One approach to the study of the genetics of allergy is a survey of restricted populations to determine not only the frequency of the various manifestations of allergy, but also the distribution of allergy in the families of those surveyed. Several studies have been done in college students since they represent a group that is alert and aware and might give more meaningful data than would other population groups. In addition, it is possible to use college students in follow-up studies for verification of some specific points. Three studies will be mentioned here to show kinds of data obtained and the way these data may be used to draw inferences.

A study by Tips[16] in a student housing project at the University of Notre Dame in South Bend, Indiana, was made up of 99 husband and wife pairs, all of whom had lived in the Midwest for at least 10 years preceding the study and who were thought to represent a random sample of the region. The data show no sex association and give strong evidence for the hypothesis that a series of recessive alleles govern the predisposition to atopy; there are separate gene pairs for each effect. Thus, hay fever, asthma, and eczema would be distinct entities involving three loci. A pool of family histories using populations other than the one in the original survey was used to test the hypotheses of three-loci involvement in hay fever, asthma, and eczema; with a penetrance correction, the separate recessive hypothesis was supported.

Van Arsdel and Motulsky[17] surveyed almost 6000 students at the University of Washington; of these, 16 per cent reported hay fever or asthma or both. There were positive family histories in only 22 per cent of the nonallergic students. Parental allergy was reported by 20 per cent of the allergic group and by only 6 per cent of the nonallergic group. If both parents were allergic, allergy was present in 58 per cent of the offspring; but if only one parent was allergic, 38 per cent of the children were allergic. If both parents were normal, only 12.5 per cent of the children were allergic.

The results of this study would support the view that allergy appears to be due to a variably penetrant recessive gene; however, the data could also be used as evidence that multiple additive genes are responsible for the allergic symptoms.

The third model study (Hagy and Settipane[5]) surveyed 1836 students at an Eastern university (Brown) and reported on those with bronchial asthma or allergic rhinitis. They found 34.8 per cent had some form of allergy; 25 per cent had a history of asthma, seasonal hay fever, or nonseasonal allergic rhinitis. Positive family histories were reported for 64 per cent of those with asthma, hay fever, or allergic rhinitis, compared with 34.8 per cent of the nonallergic students. Because the family history data in this last study did not include specific information on the status of the parents, no inferences were made which would apply to characteristics of offspring from the different parental classes.

The three studies reported here, as well as the study by Maternowski and Mathews,[11] show how locale plays a role in frequency of allergy. Although some population sampling differences may exist, a major influence on the frequency of allergies is the nature of allergens present in the different environments. The proportion of allergic individuals with hay fever and asthma (and in some cases eczema) varied from 16.7 per cent in the Northwest and 19.1 and 20.2 per cent in the Midwest, to 25 per cent in the Northeast.

In genetic studies on allergy, the selection of controls may be a source of difficulty. In the college studies, one must be certain that those who do not have allergies or history of allergy represent the same social or ethnic stratification as those who do have histories.

In family studies, sibship controls are usually considered good since the environmental component is relatively similar; but if both parents are allergic, and the recessive theory with variable expression is being tested, the difference between affected and unaffected may still be primarily nongenetic. If the disease has a genetic component, we would expect a higher incidence of affected persons among siblings of affected individuals than among siblings of unaffected individuals. The number of siblings of both affected and nonaffected types that are needed before a conclusion can be reached as to the significance of the difference between the two groups depends upon the incidence of the trait in the siblings of affected persons and the level of probability we choose to use. Although we do not need unlimited numbers or open-ended surveys in order to draw conclusions, in most published surveys we find no attempts to use statistical methods to circumscribe the study. Usually the numbers used in a survey are selected for some reason that is other than statistical; yet, in studies of this sort, it is just as important to know when to stop as to know the acceptable minimum size of the sample. The significance of the difference between groups is not going to get meaningfully greater with a larger group if it is already significant with a smaller sample. How much of a population must be sampled to have a reasonable sample of the population? It must be large enough to satisfy the statistical demand; no other mystical qualities are necessary. If 500 individuals give the answer, 10 or 100 times as many will not make the answer better. There is now sufficient information on the prevalence of allergy in a population that even limited studies, properly planned, can be meaningful. All too frequently, however, reports of single families or unusual, isolated events or poorly planned surveys which contribute little to our knowledge of the inheritance of allergy still appear in print.

In studies on the relative importance of the roles that genes and the environment play in a particular disease state, a common technique used is to compare the frequency of the disease in monozygotic (identical) and dizygotic (fraternal) twins. Twins of both classes are usually reared together, and the differences between the two types are assumed to be of primarily genetic origin. If both members of a twin pair are affected, or both members are not affected, they are called concordant. If only one is affected, they are called discordant. The purpose of the twin studies is to compare the frequency of concordance in the monozygotic twins with the frequency of concordance in the dizygotic twins. When the concordance ratio in both dizygotic and monozygotic twins is similar, it can be concluded that the trait does not have a large hereditary component and is dependent primarily on environmental components.

There are, however, some dangers in the collection of twin data. Many studies start with the proband being an affected twin. This would tend to eliminate from study any pair where neither is affected. Such bias would lead to the loss of concordant pairs and a net gain in the frequency of discordance. Another danger is inherent in the system itself; that is, reporting of twin data when concordance exists may be more common for some traits than reporting when discordance exists. Because this bias occurs when literature is searched for data and the collected reports are analyzed, individual reports should be avoided. The most satisfactory method of avoiding this bias is to study a population of twins with no prior ascertainment, and large twin populations have been so studied in Sweden. Nevertheless, the literature still accumulates individual or small twin studies in which the bias of ascertainment is overlooked.

Some questions have recently been raised as to the genetic variation that might occur in monozygotic twins, including polyspermia or mosaic formation. Although genetic differences between identical twins have been thought to be rare events and to have no significant influence on data analysis, we may have to be more cautious about making this generalization. The basis for this reservation is the finding from other genetic models of a phenomenon called dosage compensation, which will be discussed later.

One consideration in some diseases, although not necessarily in allergy, is that the fact of twinning itself may sometimes affect the growth and development and subsequent reactions of a person born as a twin. To overcome this problem, we must first compare the frequency of the trait in twins with the frequency of the trait in the single-born population. If there are stress or psychogenic factors in allergy, we may find the smaller or less aggressive twin to be more susceptible to the disease than is the single-born individual. This psychological interaction has already been suggested for schizophrenia and other forms of severe mental defects. Behavioral interaction between allergic twins would manifest itself as high frequency discordance and a frequency of allergy different from the single-birth population.

Data on twins reared apart are particularly useful in that the variability in the environmental component may be more clearly manifested. Because twins reared together have a strong tendency to choose similar life situations, they have the same environmental exposures. This is, of course, more true for monozygotic twins than for dizygotic twins – particularly in view of like sex in the former situation as compared with unlike sex in half the dizygotic twins.

An additional factor in twin studies that may have an effect on twin data analysis in general is the diagnosis of zygosity. One can quickly eliminate from the monozygotic class the twin pair that is of unlike sex. The subjective judgments of parents and friends as to zygosity on the basis of the appearance of the twin pair may not be safe enough for genetic studies; obstetrical evidence and blood, serum, and tissue typing provide information needed in classification.

The twin studies in allergy have, in general, been characterized by very small samples involving one pair or a few pairs; such studies do not add significantly to our understanding of the genetics of allergy. There have been a few notable twin studies; one by Cooke and Vander Veer[3] on six pairs of twins found in the population of 504 cases of allergy was used in 1916 as the basis of their claim that allergy is inherited as a simple Mendelian dominant trait.

Studies by Spaich and Ostertag[15] and by Bowen[2] were on a larger scale than most, and the findings in both studies were striking in the degree of discordance between monozygotic twins for allergic manifestation and severity.

A very recent study by Edfors-Lubs[1] is an excellent example of the exploitation of twin information for the purpose of elucidating the hereditary component in allergy. She used the Swedish twin registry, which included totally ascertained twins born over a period of 40 years, to select respondents for a questionnaire designed to amass data on the prevalence of allergies of various types, including asthma, hay fever, atopic dermatitis, and contact dermatitis. Her purpose was to weigh the relative roles of heredity and environment as they affect the risk of having an allergic disease. She was particularly interested in determining the elements affecting the interaction of gene and environment as defined by genetic penetrance (the appearance or nonappearance of a trait in a person known to possess the gene controlling the trait) and gene expression (the degree to which the trait manifests itself).

The analysis of her results as they address the question of the heritability of allergic diseases, that is, whether the inheritance is by dominance, recessivity, or multiple factors, is complicated by the fact that the relatively high frequency (0.18) of phenotypic allergy and the estimated penetrance (0.40) as determined by analysis of monozygous twins fit almost all theories. A part of the analysis was based on individuals who had asthma, hay fever, or eczema; in addition, analysis was made of the group enlarged to include all of the above as well as those with contact dermatitis. The hypotheses of dominance, recessivity, and multigenic inheritance were all supported by the data; however, the variability in number of symptoms in an individual made the multiple factor theory most reasonable.

Of more direct interest to the clinician than the mode of inheritance is the risk of having a child with allergy. This risk estimate can be derived

Table 1. *Risk of Allergy in First Degree Relatives of Allergic Individuals**

		RISK (PER CENT)	
PROBAND	ALLERGY	*Normal Population*	*First Degree Relatives*
ASTHMA	Asthma	3.8	9.2
	Hay Fever	14.8	25.2
	Eczema	2.5	4.3
HAY FEVER	Asthma	3.8	6.0
	Hay Fever	14.8	24.1
	Eczema	2.5	3.3
ECZEMA	Asthma	3.8	6.2
	Hay Fever	14.8	24.1
	Eczema	2.5	7.7

*Modified from Lubs, M. L.: Empirical risks for genetic counselling in families with allergy. J. Pediat., 80:26, 1972, by permission.

Table 2. *Risk of Allergic Child Based on Condition of Parents*

a. Calculated risk based on estimated gene frequency derived from 18% prevalence; 40% penetrance (Lubs)

PARENTS	FREQUENCY OF PARENTAL TYPE (%)	RISK OF ALLERGIC CHILD (%) *Recessive Hypothesis*	RISK OF ALLERGIC CHILD (%) *Dominant or Multifactor Hypotheses*
POS × POS.	3.2	40	32.7
POS × NEG	29.5	27.6	28.5
NEG × NEG	67.3	14.3	13.7
NEG × NEG + Previous Affected Child		19.0	24.9

b. Empirical risk based on students' knowledge of parental types (Van Arsdel and Motulsky)

PARENTS	FREQUENCY OF PARENTAL TYPES (%)	RISK OF ALLERGIC CHILD (%)
POX × POS	.85	58
POS × NEG	14.5	38.4
NEG × NEG	84.0	12.5

either from empirical data, that is, what has already happened to others, or from derivative data, determined by calculation and extrapolation from interpretations of observed data.

The empirical risk information determined in the large twin study by Edfors-Lubs[4] was summarized in a second paper (Lubs[9]) to show normal risk for various types of atopic disease, as well as the increased risk in first degree relatives. For example, if an individual has asthma, the risk of a sibling or child having asthma is 9.2 per cent rather than the expected 3.8 per cent. A portion of her risk data is shown in Table 1.

The risk of having a child with allergy when there is information on both parents can also be determined (Table 2). This risk has been calculated by Edfors-Lubs from the data on prevalence of allergy and the degree of concordance between identical twins; there is no direct knowledge of the state of the parents. The various classes of matings were based on the estimated frequency of the allergy genes in the population and the probability of allelic combinations in any two parents.

On the other hand, Van Arsdel and Motulsky,[17] in their survey of students, also elicited information about the state of the parents; the risk figures they cite represent real numbers, subject, of course, to any response errors made by the students.

If one leans toward the multiple factor theories of allergy, the empirical data of Van Arsdel and Motulsky[17] are more appropriate for counseling. In any case, whether the calculated or observed risk figures are used, the sets of data may not accurately reflect the regional variation for allergic prevalence. The Edfors-Lubs[1] calculations are based on the Swedish twin population, and the Van Arsdel and Motulsky[17] data are based on a population tested in the state of Washington; the environmental factors, such as degree of exposure to allergens, are impossible to quantify for a universal set of risk figures.

Edfors-Lubs[4] has included in her paper various estimates of the prevalence rates of atopic diseases as gleaned from the literature. Table 3 shows the prevalence rates determined in the four studies on college populations which we have already mentioned. Each prevalence figure should lead to different estimates of gene frequency or different estimates of penetrance as influenced by the environmental components in allergy.

An attempt to answer the question of the mode of inheritance of allergy is made not only to satisfy intellectual curiosity or to improve the counseling that a physician may offer a patient, but also to delineate the possible mechanisms for the allergic state.

If we first suggest that allergy is inherited as a single recessive or a single dominant gene, we imply that the difference between an allergic and a nonallergic individual must be a single step in what is probably a complex set of pathways. The step is under genetic control and alternate forms of the gene (alleles) affect that step. The normal gene may forbid a process from occurring or may be active as a structure or enzyme in initiating or continuing the stepwise process. The abnormal allele – the gene which is the gene for allergy – would either permit a forbidden step or inhibit a necessary step. Again, we must visualize how genes act. They are responsible for the formation of a protein which acts as a functional structure or as an enzyme catalyzing a particular step in a biochemical pathway. In the sense of the classic one gene–one enzyme concept or the modern one gene–one polypeptide concept, each gene is responsible for a unique product that has a role in homeostasis. A mutant gene is an allele whose product is not usually adequate to match the ability of the product of the normal gene in maintaining the homeostatic state which evolved over an incalculable period of time. Indeed, most mutant genes are selected against simply because the individual with a gene mutation at an essential locus may not be as biologically successful as the individual with the normal gene.

Since there are several hundred thousand loci in man and mutation occurs at a rate varying from 1 per 100,000 to 1 per 1,000,000 cell generations, the process of evolution is continuous. It is actually the process in which mutant genes, normal genes, and the total environment interact to

Table 3. *Prevalence of Allergic Rhinitis and Asthma in Different Populations of College Students*

INVESTIGATOR	SITE	PREVALENCE (%)				
		Allergic Rhinitis	*Asthma*	*Both*	*Allergy*	NUMBER
Van Arsdel and Motulsky	University of Washington	12.0	2.0	2.7	16.7	5818
Maternowski and Mathews	University of Michigan	13.4	2.5	3.2	19.1	434
Hagy and Settipane	Brown University	19.7	1.4	3.9	25.0	1836
Tips	Notre Dame University	16.2	1.6		20.2	198

determine, empirically, whether the mutant gene will be retained or lost to the next generation.

In the one-gene theories for allergy, the difference between a dominant theory and a recessive theory may reflect the nature of the gene action involved in the allergy. In man, most deleterious dominant traits, such as polycystic kidneys, multiple polyposis, achondroplasia, and Marfan's syndrome, are caused by the mutant gene's producing some structural abnormality that affects structural development, rather than by the mutant gene's producing an altered, ineffective enzyme. The recessive diseases are usually caused by the lack of effective enzymes, such as occurs in phenylketonuria, albinism, Tay-Sachs disease, and galactosemia, or the lack of effective functional units or products, such as occurs in sickle cell anemia, Wilson's disease, and agammaglobulinemia.

A few implications of the single-gene theories which involve only the level of the initial antigenic stimulation may be suggested. The dominant theory may imply the direct loss of structural integrity and a consequent sensitization by the presence of the allergen in a forbidden site or a forbidden condition. The recessive theory may imply the presence of an enzyme or a product that fails to inhibit or fails to reverse the coupling of the allergen with body protein and thus allows the hapten protein complex to form and induce sensitization. The dominant theory would allow for the existence of a changed protein which can couple easily with the haptenic allergen.

We could go on to devise theoretical structural or enzymic conditions to account for allergy in any other step which we recognize as playing a role in the immune response up to the formation of mediators and the responsiveness of tissues to the mediators. In other words, while conjectural, the inheritance pattern must control each step in the allergic sequence.

"Multifactorial inheritance" implies that there is potential for mutant alleles at several loci and that the final manifestation of allergy is an outcome of a series of small additive genetic effects. An alternative interpretation is that in a series of steps, each under genetic control and each playing a part in maintaining a nonallergic state, a mutant gene at any one of these loci would make an individual vulnerable to one or more than one allergen.

Every theory for allergy must include the role of variation between individuals resulting from alternative forms of genes in the population. All activities of cells, and thus of tissues, organs, and individuals, are the effect of the turning on or turning off of specific genes in the cells by other genes or other intrinsic or extrinsic environmental components. We do not minimize the environmental influences on allergy, either in terms of the presence of the allergens in the air or the exposure of the individual to the developmental or psychological variables in life; but we must not exclude genes as an essential component in allergy.

Those variations in the manifestation of traits which we call penetrance and expressivity are generally poorly understood from a mechanistic point of view. The degree of penetrance is derived from the data on occurrence of allergy coupled with the single dominant or single recessive gene theory and is simply the mathematical term which accounts for the discrepancy between theory and observation. If we accept a single-gene theory, we must hypothesize that there are other, perhaps minor, genetic loci which affect the rate of hapten-protein coupling or which influence the rate of immune globulin synthesis or mediator synthesis. The environmental component in penetrance may be length of exposure, age of first exposure, or variety of allergens in the environment. Nor can we overlook the fact that other genes are part of the penetrance and expression equation.

Not to have allergy may be the active process; breaking the sequence of steps makes allergy the passive process. If allergy is an active process, many steps are involved; the twin studies suggest the number of subtle components of gene-environment interaction. Monozygous twins are identical in genotype, but the phenotype is the result of gene interaction with environment, an interaction that may yield, in the same situations, either the barrier to or the inhibition of the continuing process leading to allergic manifestation.

A list of the allelic interactions that can lead to different effective genomes must include allotypic allelic exclusion, the Mary Lyon effect (X chromosome inactivation) and perhaps other forms of dosage compensation which are not recognized as major gene effects. Therefore, identical twins are identical only in terms of initial genome but not necessarily in phenotype. If the forms of allelic exclusion or dosage compensation are decided very early in tissue differentiation and the twins are heterozygotes at many loci, then the random turn off of an allele at a locus or a segment of chromosome would lead to essentially different phenotypes in two individuals with the same genome but with different alleles turned off or on.

One may even postulate that there is no environmental factor in discordance between identical twins reared together but that in multiple heterozygotes the random choice of the alleles turned on or off is the significant source of individual variability. This postulate implies genetic non-identity of monozygous twins at the cellular level.

A single-gene theory in the narrowest sense may imply that non-allergy is an active condition in man. The allergic state results from the failure of the product of the mutant gene to inhibit a step which prevents allergy. The active theory of non-allergy may imply that only one single step in the process is the vulnerable step. The variation in penetrance and in the expression of the allergy in terms of allergen or syndrome is a factor of subtle influences of intrinsic and extrinsic environment on development.

The explanation of variability in penetrance and expressivity in purely genetic terms based on a one-locus theory would imply that there are, in reality, one major locus and one or more minor loci in the development of allergy. This implication would then force the rejection of a single-locus theory.

If non-allergy is a passive state, the development of allergy in the presence of variant genes at a single locus is due to the initiation of an active process which starts at exposure, continues through sensitization, and ultimately leads to the tissue response. The single-gene theory would imply that the whole process must proceed to completion once activated.

For example, if the variant gene leads to a protein configuration which easily binds the allergen, then an effective antigen may be formed. If the variant involves IgE synthesis, the variant may lead to a qualitatively or quantitatively different IgE, which is the agent responsible for the steps leading to mediator release.

As a result of mutation and the retention of mutant genes in the populations, a large amount of genetic variation exists in man. The gene mutations producing disease represent only a small proportion of the mutant genes in man.

The term *genetic polymorphism* was defined by E. B. Ford as "the occurrence together in the same habitat of two or more discontinuous forms of a species in such proportions that the rarest of them cannot be maintained merely by recurrent mutation." The concept of polymorphism is useful in understanding either the single gene or the multifactorial basis of the inheritance of allergy. What is implied by polymorphism in relation to allergy is that the gene or genes responsible for the allergic response have provided forms of variability necessary for man to adapt to environmental change. The polymorphism arises by mutation, which is a random process, but the selective effect of the mutant gene on an individual must be negative (the most common event), neutral, or advantageous. If the mutant is negative in its survival value, it will be selected against. If the mutant gene is neutral, it is just barely maintained; its very low frequency will be constant, and the gene will not spread widely in the population. In order for polymorphism to develop, the mutant gene must have some selective advantage. The fact that the mutant gene has not completely replaced the original gene means that a balanced or stable polymorphism has been established and that the discontinuous variation is advantageous to man.

Polymorphism is usually maintained through selective advantage of the heterozygotes over both homozygotes. An unusually good example of polymorphism in man is seen in the allelic genes controlling hemoglobin structure. A single locus controls beta-chain synthesis, and there are two major alleles at this locus – the A allele, which gives rise to the normal hemoglobin molecule, and the S allele, which gives rise to the abnormal hemoglobin (sickle hemoglobin). The individual who is heterozygous AS makes both normal hemoglobin and sickle hemoglobin and generally has no problems in maintaining normal life. The individual homozygous for S hemoglobin has sickle cell anemia. The hemoglobin locus is one example of how polymorphism works in selection because in the presence of falciparum malaria, there is selection against homozygous A people; the homozygous S individual is also strongly selected against since he does not generally live to reproductive age; the heterozygote is the survivor and the propagator of the species. As a result of the loss of the homozygous A and the homozygous S individuals, the heterozygote, AS, is more likely to have children and thus maintain the frequency of the A gene and the S gene in a stable ratio.

With the sickle cell story as our model, it is not unreasonable to assume that a single gene controlling allergy plays or has played a significant role in man's survival and evolution.

We will discuss later some of the polymorphisms that are known to affect aspects of the immune response and from these polymorphisms we will develop evidence that allergy is inherited as a multifactorial system that includes several loci, each locus playing a role in the acquired response of an individual to a factor or factors in the environment.

In looking at allergy as a polymorphism, we would like to study the environmental differences between a particular polymorphism and specific allergies; in reality, however, it is difficult to find the selective advantage of allergy on man's survival and evolution.

Since allergic diseases can be considered altered immunologic responses, the polymorphisms in man that are associated with immunologic systems should be examined in an effort to determine whether the total or additive effect of immunologic variability can account for allergic reactions. The immune response is itself a multifactorial genetic system, but any single step may be the basis of nonresponsiveness.

The allergic reaction begins with the exposure of a susceptible genome to an allergen. The age of primary exposure, the dose of the exposure, and the nature of the exposure represent the environmental components of the primary antigenic stimulus.

The metabolic pathway for the processing of the antigen represents recognition and the stimulus to response. The total of the response is a factor of the ability of the immunologically competent cells to respond. The ability to produce specific classes of antibody, to mobilize specific cells and to form the mediators that cause the ultimate symptoms are all necessary components in the allergic response.

If we wish to accept a multiple gene theory for allergy and if we are prepared to accept the assumption that there are many polymorphisms in man, we can look for support to some of the examples of polymorphism involved in all aspects of the immune response. In this discussion, we will not be concerned with immunologic deficiency diseases since they are not true polymorphisms. We will consider only those polymorphisms that exist with fairly high frequencies and that represent variants around normal values of responsiveness.

The first well-recognized polymorphism in man is the A, B, O blood-group system; although there is no evidence of association of blood type with allergy, the system is a useful model of polymorphisms of immunologic significance. In past years, evidence was collected for and against the idea that certain blood types correlate with higher frequencies of specific diseases. For example, there is a higher frequency of gastric carcinoma in type A individuals than in type O individuals. There is a higher frequency of duodenal ulcer in type O individuals than in type A individuals. As part of the argument for selective value of blood group genes, the mechanism of selective susceptibility to the disease state must involve characteristics of the blood groups; but, in general, there are not clear one to one relationships. Nevertheless, the frequency of the A, B, and O genes in the population is indicative of the selective role blood groups played at some time in man's history.

The presence or absence of a specific natural antibody can also be considered evidence of polymorphic variation in man. The anti-A or anti-B present in man affects the response of individuals to certain antigenic determinants. Indeed, the presence or absence of the A or B antigens also affects antigen recognition and represents in a broad manner the responder-nonresponder effect of an immune response gene.

The polymorphic systems involving cell antigens in which complex genetic systems are involved include the Rh antigens and the MNS family of antigens. Although there is no evidence that these loci have an effect on the immune response to antigens outside of each system or that they correlate with disease susceptibility, they too must have played a role in man's evolution and they may still have a subtle role in selection.

The tissue compatibility systems, recently subjected to intensive investigation, have been found in man and in certain experimental animal systems to be associated with immunological properties other than tissue specificity. The major compatibility system in man, called the HL-A system, includes a large number of alleles that control arrays of antigens which have a role in acceptance or rejection of transplants. In addition, there have been reports that the HL-A genes either themselves or as markers of adjacent regions of the chromosome may affect immune response to antigens not apparently related to tissue compatibility. (For more detail of this association, see the review by McDevitt and Benacerraf.[12])

The model which stimulated these investigations was the major tissue compatibility system in the mouse, the H–2 system. The region of the chromosome in which the H–2 genes appear to reside also contains a series of genes, called IR genes, which affect the response or nonresponse of particular strains of mice to synthetic polypeptide antigens and to very small doses of some protein antigens (see Levine and Vaz[7]). This chromosomal segment also has the MLC locus, another recognition unit, as well as a locus controlling an antigenetically distinct serum lipoprotein.

Marsh et al.[10] and Goodfriend et al.[14] have reported evidence that the response to purified ragweed antigen, Ra5, is associated with the HL–A7 related alleles of the human tissue compatibility locus. Levine, Stember, and Fotino,[8] extending earlier studies on H–2 alleles and reagin production in mice, have found that an immune response gene for the E antigen of ragweed was present in 7 human families and was associated with particular HL–A haplotypes. This association was demonstrated by the facts that HL–A 1, 8 was necessary but not sufficient for high IgE response, and that the presence of the allele also correlated with clinical hay fever. The system suggested by Levine[8] has at least two components – one is the IR–antigen E gene associated with the haplotype and the other is a genetic system which permits a high reagin response.

The environmental component is an essential element in the allergic response and includes adequate exposure to the allergen and the movement of the antigen through mucous membranes to ultimately reach immunocompetent cells. The work described in these papers delineates genetic control of at least two steps in the process of allergic sensitization. Additional polymorphic systems which are directly associated with allergy may exist and may include the following:

1. receptor sites on cells for IgE fixation,

2. the extent of response by the cell to the allergen complexing to the attached IgE,
3. the nature and amount of the mediators that are produced in an individual,
4. the sensitivity of tissues to mediators, and
5. the nervous system components controlling the extent of symptoms in the affected individual.

Polymorphic systems not yet associated directly with the allergic response include the complement system and the genetic variations in antibody demonstrated as allotypes or idiotypes.

The variants in the complement system consist of structural heterogeneities which appear to be harmless, although they still might be responsible for the differences in individual response to allergic challenge. (See review by Alper and Rosen.[1]) There are specific diseases which have their basis in abnormalities of the complement system. For instance, angioneurotic edema, transmitted as an autosomal dominant trait, results from a defect in the synthesis of the C1 esterase inhibitor. This genetic defect is not a true polymorphism and does not play a role in the variability of allergic reactions in normal populations.

There have been reports of C2 deficiency in several families, but there is no recognized effect of this deficiency in delayed or immediate hypersensitivity.

The C3 polymorphisms in man have been found as variants in electrophoretic behavior and also as variants in a passive hemagglutination system. There appear to be three variants controlled by two alleles. As yet, there are no physiologically detected effects of any of the variants.

Although other variants in the complement system have been reported, there has been no clear evidence that they are the result of direct gene action.

The allergic reactions may involve all or some of the mediators which have been found to result from antigen-antibody reactions in vivo. These pharmacological agents have been tested in animal models and variations in response have been noted. Thus, components of allergy may well belong to the realm of that special area of genetics known as pharmacogenetics, which is defined as the study of genetically determined variations that are revealed by the action of drugs. Drug "allergy" may be based on differential sensitivity to the action of the drug itself and not necessarily on the alteration of the immune system. In the terms of pharmacogenetics, the drug may have an unusual, prolonged, profound, or no effect on a specific tissue or cell.

CONCLUSIONS

We have attempted to demonstrate that the assessment of the role of heredity in allergy must not stop at the level of the proof or disproof of a hypothesis on the mode of inheritance of allergy based on pedigree, population, or twin studies. One must recognize that the support of a theory on inheritance also requires acceptance of the corollary of such a theory—i.e., the fact that inheritance is simply the way the genes get from generation to generation. The business of the gene is to play a role in physiologic activity at all levels, from the cell to behavior, and the question of single gene versus multigenic effects has direct implications as to the mechanisms behind the atopic response. If one supports the theory of polygenic inheritance, then one must recognize the need to discover the individual loci involved and the contribution of each locus to the mechanism of the allergic response. If one supports a single gene inheritance theory, then one must recognize that the locus involved activates or fails to inhibit a process which, when completed, results in the manifestation of allergy. There also remains the need to understand the nature of environmental components and the interaction of the environment with the genome to produce differences in response in the two apparently identical genomes we see in monozygotic twins. We have made no attempt here to account for the role of age, infection, or emotional factors as separate from the unknown we call the environmental component in allergy.

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Rhinitis

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IgE-MEDIATED RHINITIS

IgE-mediated rhinitis refers to the antigen-induced, antibody-mediated, hypersensitivity reaction which occurs in the nose. Synonyms are perennial allergic rhinitis for continuous nasal disease and seasonal allergic rhinitis for transient symptoms caused by exposure to seasonal aeroallergens. Seasonal rhinitis is frequently called hay fever by both laymen and physicians. IgE-mediated rhinitis results from the reaction of antigen with IgE antibody fixed to the surface of mast cells in nasal tissue with resultant release of vasoactive mediators. The immunologic mechanism distinguishes IgE-mediated rhinitis from rhinitis which is not the result of antigen-antibody reactions, even though the clinical symptoms of both types may be similar.

Allergic rhinitis is a significant medical problem because of its incidence, as it involves 10 per cent of the population; its duration, since symptoms may last for months or even the entire year; and the continuance of the disease state since it may begin in early childhood and persist for most of a patient's life. Although the symptoms of allergic rhinitis may be considered trivial or even humorous by those not afflicted, they can be associated with significant local discomfort and generalized symptoms of malaise and fatigue.

Finally, rhinitis may be associated with or cause complications including sinusitis, otitis media, and nasal polyposis. These characteristics of allergic rhinitis in the general population result in a significant investment in symptomatic medication, and a large number of visits to the physician and days missed from work or school.

Mechanism of the Disease

The chain of events which results in the symptoms of IgE-mediated rhinitis is relatively clearly understood. The description of these mechanisms which follows is based both on experimental evidence from human studies and presumptions resulting from various in vitro and in vivo studies which appear applicable to man.

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IgE-mediated (allergic) rhinitis is an immunologic disease of the Type I, anaphylactic hypersensitivity as defined by Gell and Coomb.[2] The initial sensitization of the individual probably occurs as a result of inhalation and absorption of small amounts of airborne antigens over a period of time. These antigens, sometimes termed allergens, stimulate the production of antibodies of a special type. For many years, these antibodies were called reagins.[*] This reaginic antibody response to aeroallergens occurs in a limited percentage of the population termed atopic subjects. The term atopic means "out of place," in this case denoting an unusual or unexpected reaction which does not occur in a majority of the population. Atopic individuals number 10 to 30 per cent of the population depending on the reported series and the criteria for evaluating the subjects. Although nonatopic subjects may develop reaginic antibodies to such injected antigens as penicillin, insulin, and hymenoptera stings, atopic individuals appear, for reasons that are not understood, to develop these antibodies against a variety of inhalant or food antigens which must be absorbed in relatively small concentration, primarily through mucosal surfaces.

Human reagins are now recognized to be antibodies of the E immunoglobulin class. Although rodents produce reaginic antibodies of immunoglobulin classes other than IgE, there is minimal evidence that certain human reaginic antibodies may reside in other immunoglobulin classes. For practical purposes, human reaginic antibodies may be considered to be of the IgE type. These antibodies are produced by plasma cells, appear in the serum, and sensitize peripheral blood basophils, tissue basophils, and mast cells throughout the body. The sensitized cells are capable of reacting with specific antigens because of the IgE antibodies which have fixed to receptor sites on the cell surfaces. They are present in the nasal mucosa and participate in inducing rhinitis by the following sequence of events.

Antigen is inhaled and is deposited on the nasal mucosa. If the antigen is ragweed pollen it is thought that the soluble ragweed antigens are eluted from the pollen by nasal secretions. These antigens pass through the nasal mucosa to react with IgE antibody fixed to the surface of mast cells in the nasal tissues. The reaction of antigen with IgE fixed to mast cells results in mast cell degranulation and release of chemical mediators. Histamine is one of these mediators and is perhaps the most important in allergic reactions in the nasal mucosa. Other mediators of potential significance include slow reacting substance of anaphylaxis (SRS-A), bradykinin, the prostaglandins, and the eosinophil chemotactic factor (ECF). The significance of these in relation to IgE-mediated nasal reactions is uncertain but the first three of them are well known to be vasoactive and could alter the vascular bed of the nasal mucosa. Eosinophil chemotactic factor released in the nose during an allergic reaction may result in the nasal eosinophilia that is so characteristic of allergic rhinitis.

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[*] Meaning, loosely, to react.

The histamine or other vasoactive mediators released in the nose following mast cell degranulation induce vasodilation and increased capillary permeability. Swelling of the nasal mucosa and tissue edema occur, owing to the leakage of intravascular fluid into tissues following the change in vascular permeability.

Symptoms of IgE-Mediated Rhinitis

Symptoms of the disease include nasal congestion, generally described as nasal stuffiness, rhinorrhea or a clear watery discharge, unless there is an associated bacterial infection, and sneezing. Other symptoms include pruritus of the nose and throat, particularly the soft palate. The rhinitis is frequently associated with allergic conjunctivitis, with symptoms of pruritus and excessive lacrimation. Any or all of these symptoms may be present in varying severity in individual patients and the whole symptom complex may vary in intensity depending on the degree of sensitivity of the patient and the amount of antigen to which the patient is exposed. For example, one patient highly sensitive to ragweed antigen may have acute, very severe symptoms during the peak of the ragweed pollination season. A different patient with mild sensitivity to house dust may have minimal, chronic symptoms throughout the year, because of exposure to house dust antigen.

In addition to local nasal and ocular symptoms just described, some patients may have systemic manifestations associated with the allergic rhinitis. These are frequently unrecognized by physicians, who are more familiar with well-defined nasal symptoms. The systemic symptoms associated with rhinitis consist of fatigue, irritability, depression, or malaise in varying degrees. The malaise which occurs in some patients may have been the origin of the "fever" portion of the term "hay fever," a misnomer, because uncomplicated rhinitis is not accompanied by fever. Allergic rhinitis may be associated with clinical manifestations of allergy of the lower respiratory tract owing to inhalation of the same antigen; if so, symptoms will include the cough of allergic tracheitis and the wheezing dyspnea of reagin-mediated asthma.

Antigens Important in IgE-Mediated Rhinitis

The antigens (allergens) important in allergic rhinitis are airborne substances to which the atopic patient becomes sensitized. These aeroallergens are generally protein substances, and certain of them, such as the major antigen of ragweed pollen, have been obtained in relatively pure form. The latter is ragweed antigen E, a protein with a molecular weight of 38,000.[1] Most other individual antigens important in allergic rhinitis have not yet been characterized and some aeroallergens, such as mold spores, are recognized as being important only by correlation of their concentration in the air with the patients' symptoms and skin reactivity.

The characteristics of those pollens which cause allergic rhinitis are that they are airborne in relatively high concentration and are produced by plants that disseminate their pollen by means of wind currents. Pollen from plants that are insect pollinated are heavier and do not constitute a significant cause of allergic rhinitis. Even though patients may be reactive to such pollen, the concentration of these pollens in the air is not sufficient to produce the nasal reactions that occur from the aeroallergens of wind pollinated plants.

The major types of pollen aeroallergens in the United States are those of trees, grasses, and ragweed plants. The concentration of pollen from these sources varies with the geographical area and this is important both in the production of the patients' symptoms and in the establishment of the cause of the rhinitis.

The physician involved with more than the symptomatic care of allergy patients in practice should be familiar with the aeroallergens present in the geographic environment of his patients, the seasonal period of pollination and the relative concentrations of these aeroallergens. The tabulation of these is beyond the scope of this article, but this information is readily available from other sources.[1, 6-8] For example, in the upper midwestern portion of the United States, trees pollinate in early spring, grasses pollinate in late spring and early summer, and ragweed plants pollinate primarily from August 15th to October 1st. Patients with seasonal rhinitis from one or more of these different aeroallergens should present a history of symptoms that correlates with these pollination seasons.

Mold spores and house dust antigen are two other major causes of rhinitis. Mold spores are derived from saprophytic fungi and are present in the air in significant concentration when climatologic and seasonal factors are most appropriate for the growth of the fungi. These conditions occur when suitable culture media such as decaying vegetation in the fall or spring combine with sufficient rainfall to provide adequate moisture. In the upper midwest, mold spores are present in greatest concentration in the spring, midsummer and fall. The mold spores decrease when climatic conditions are inappropriate for optimal growth or environmental culture media are decreased or largely absent, e.g., in midwinter when snow is on the ground and covers dead vegetation.

Delineation of mold sensitivity by history of seasonal symptoms is more difficult than that of the well-defined pollen seasons and requires that the physician be familiar with the seasons when mold spores are maximal in the geographic area of his practice. An additional aid in the diagnosis of mold allergy is the correlation of symptoms with places of high mold concentration. These include barns, because of mold growing in hay or straw, and damp basements. Patients with mold allergy may observe an increase in symptoms following mowing of lawns with a rotary mower and attribute it, incorrectly, to grass pollen allergy, when actually the mold growing in soil underneath the grass, being forced into the air, causes the respiratory symptoms.

House dust antigen constitutes a major source of general environmental allergen. It is derived from household environments and is not outdoor dust, such as road dust. Although considerable evidence indicates that house dust mites, particularly Dermatophagoides pteronyssinus, produce or are a major antigenic component of house dust,[1] sources of house dust antigen might not be uniform, but vary from patient to patient. Symptoms from house dust are generally perennial since this antigen is obviously present in a patient's environment throughout the year. A common occurrence in northern climates is an increase in symptoms during the winter in house dust sensitive patients. This is explained by the increase in environmental house dust antigen exposure associated with closed environments, increased use of bedding, recirculation of air in houses due to forced air furnaces and decreased humidity. Patients with house dust allergy often give histories of an increase in symptoms during high dust exposure during house cleaning, vacuuming, moving stored bedding and clothing or in library stacks.

Certain antigens are not present in all environments but can be significant causes of allergic rhinitis. The most important of these antigens is animal dander. Animal antigens are the materials derived from the epithelial surface or saliva of animals. Although many patients consider animal hair the significant factor, the insoluble nature of hair makes this a poor source of animal antigens and the important dander antigens are the soluble materials, largely proteins, which are derived from the skin or secretions of the animals. These antigens permeate the patient's home environment and become a component of house dust. They are often not recognized by patients. Although cats and dogs are the major source of animal danders, other pets are often exempt from suspicion in the patient's mind as a source of animal dander. Gerbils, guinea pigs, birds, hamsters, rats, and mice kept as pets, particularly in a child's bedroom, can be a major cause of symptoms. A patient or parent may disregard these pets as sources of antigen because of their small size. Their importance becomes obvious in occupational exposure where such animals can be significant causes of respiratory allergy among laboratory workers. Other antigens which may be causes of rhinitis are materials to which a patient is exposed during occupational activities, and information about such exposures must be obtained while taking the allergy history. Patients with such occupational allergies are generally better on weekends and asymptomatic on vacations.

The question of food allergy as a cause of IgE-mediated rhinitis is frequently raised but food allergy is rarely a cause of rhinitis.* The reason for this will become obvious if it is recognized that, in allergic rhinitis due to identified allergens, the allergens such as ragweed come into direct contact with the nasal mucosa. The opportunity for ingested antigens to contact the nasal mucosa directly is minimal, and absorption of antigens through the gastrointestinal mucosa, and their passage through the circulatory system to the nasal mucosal mast cells in extravascular areas without reacting with circulating antibodies, is not likely.

Certain exposures of patients with allergic rhinitis to nonspecific (nonimmunologic) stimuli are followed by an increase in nasal symptoms. Examples are tobacco smoke, perfumes, newspaper print, and alcohol. These are nonantigenic stimuli which can enhance the nasal response in IgE or non IgE-mediated rhinitis. These responses are often mistakenly interpreted as allergic responses by patients (and by some physicians) rather than as nonallergic, nonspecific stimuli.

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*A possible exception to this general rule is the fairly common sensitivity of certain hay fever patients to cucumbers and melons during the season but not during the remainder of the year.

Diagnosis

The diagnosis of IgE-mediated rhinitis is based on history, physical examination, eosinophilia, and demonstration of IgE antibodies as a confirmatory diagnostic aid. By far the most important diagnostic feature is the history. This should elicit the typical symptoms, the seasonal relationships of the symptoms, and precipitating antigens described above. Thus an appropriate history establishes not only the diagnosis but also the antigen or antigens of etiologic importance. Examination of the nose (during a symptomatic period) usually shows a characteristic nasal mucosa which is pale, bluish, and edematous. There is a clear, watery rhinorrhea unless a purulent infection is coincidentally present. Conjunctivitis may be an associated finding. Peripheral blood eosinophilia during a symptomatic period may range from 300 to 800 eosinophils per cu. mm. (about 4 to 11 per cent of the differential count) but is rarely higher. Microscopic examination of the nasal secretions (e.g., with Hansel's stain, which is easy to use and differentiates eosinophils well) should show eosinophils, but a secondary infection might obscure the eosinophilia by the invasion of neutrophils. The establishment of the diagnosis by history and the delineation of the significant antigens, also by history, is followed by a demonstration of IgE which confirms the diagnosis.

Skin Testing and Other Diagnostic Aids

Skin tests in IgE-mediated diseases remain one of the most useful aids in diagnosis. They are also one of the most abused and misunderstood tests in the practice of medicine. They are covered in one of the other articles in this issue of the *Medical Clinics*.

The advances in knowledge of the immunology of the IgE class of serum proteins and the availability of IgE myeloma proteins for development of specific immunochemical reagents has led to the development of radioimmunoassay techniques for detection of IgE antibodies by laboratory rather than skin test techniques. The radioallergensorbent test (RAST) is such a laboratory technique.[10] The test is specific but, in its present form, takes 3 to 4 days, which is too time-consuming for clinical usefulness. At any rate, it will not replace the appropriate history and physical examination in establishment for the appropriate diagnosis. Other types of solid phase radioimmunoassay for IgE antibodies[5, 11] have been developed but are used as research techniques because sensitivity is less than cutaneous test procedures.

In a common clinical disease such as IgE-mediated rhinitis, in which diagnosis and treatment has not been perfect, it could be expected that the search for simple and reliable diagnostic tests would continue. A variety of poorly defined techniques such as the "cytotoxic" tests have been proposed: presumptively, these tests demonstrate morphologic changes in leukocytes to which antigen has been added. Provocative skin challenge is another of these questionable techniques. The provocation is the injection of food or other antigens in the skin with the attempt to produce nasal symptoms. These tests, and others like them, have no sound theoretical basis, nor have they been tested in controlled clinical trials to warrant their use in clinical allergy. Physicians in any specialty or general practice who are involved with the diagnosis or treatment of allergic diseases and who consider using such techniques should first look closely at the scientific support for them. The field of IgE-mediated allergy has now reached a level where scientific support for any such proposed methodology is available and should be required before they are recommended for clinical use. The standard practice for diagnosis of IgE-mediated disease continues to be based on the allergy history, physical examination, and appropriate use of skin tests.

Treatment

Treatment of IgE-mediated rhinitis includes specific and symptomatic therapy. Specific therapy refers to measures that inhibit or prevent the specific, antigen-induced, IgE-mast cell-mediator-release events which produce symptoms. The most important measure is avoidance of antigen and this can be remarkably successful in certain cases. A patient with severe IgE-mediated rhinitis due to a single allergen such as cat dander will become asymptomatic if the cat is eliminated (and the cat dander is removed by cleaning or disseminates naturally from the environment). Avoidance of other aeroallergens is usually difficult and requires considerable effort. Control of exposure to pollen antigens, in particular, is virtually impossible for patients who cannot take "hay fever-vacations." Moderate success in the control of house dust antigen is possible with the following measures. Encasing patients' pillows and mattresses with plastic or airtight covers, elimination of rugs and dust-collecting items in bedrooms, cleaning furnace filters, and maintenance of adequate humidity in homes will reduce dust concentrations in home environments and often significantly relieve patients' symptoms. Even "near-perfect" control is only relative, however, since it is obvious that an ubiquitous antigen such as house dust cannot be completely avoided.

Specific therapy also attempts to alter the degree of IgE-mediated reactivity of the patient by parenteral injection of the antigen to which the patient is sensitive.

This type of therapy, currently termed immunotherapy, is discussed elsewhere in this series of articles and methodology is described in standard texts.[1, 6, 8]

Symptomatic therapy for control of rhinitis is relatively successful and controls minimal to moderate symptoms sufficiently so that many patients can live a comfortable life during the periods of seasonal rhinitis or even with perennial rhinitis.

Antihistamines constitute the major drug in current use for the symptomatic control of rhinitis. They are relatively effective in control of the sneezing and rhinorrhea of allergic rhinitis and also control allergic conjunctivitis to a lesser extent. They are thought to act as competitive inhibitors for histamine at receptor sites on reactive cells. However, the exact method of action is uncertain and the antihistamines do not block all cellular activities of histamine. Because of their mechanism of action, for these agents to act most effectively, they must be given prior to histamine release and attachment of histamine to the cell receptor sites. Therefore, chronic use during the pollen season or persistently for the patient with perennial rhinitis is the most appropriate method of administration.

There are two major limitations in the use of antihistamines for allergic rhinitis. One limitation is their failure to achieve complete control in many patients. This may be due to inadequate tissue levels of drugs at cell receptor sites, the possible importance of mediators other than histamine which are not blocked by antihistamines, or other unknown factors. The second major limitation is their side effects. Although they may have an excitatory effect on the central nervous system in some patients, the more common effect is depression The resulting somnolence is a major complaint in many patients and is particularly evident with diphenhydramine, one of the most effective antihistamines available for clinical use. Finally, the antihistamines may have other side effects[3] and may appear to lose effectiveness with prolonged administration.

Because there are about 50 different antihistamines and a large percentage of these are available for clinical use, physicians should become very familiar with a few of them, preferably one of the three different major classes (ethanolamines, ethylenediamines and alkylamines). Representative antihistamines of these three classes include diphenhydramine, tripelennamine, and chlorpheniramine, respectively. These agents may be used on a regular basis through the day, dispensed in a time-release preparation or in combination with sympathomimetic agents as described below.

The sympathomimetic drugs with primarily alpha-receptor activity are effective vasoconstrictors of vessels of the mucosal surface and have been used as topical agents in the nose for reduction of rhinitis from a number of causes, including infectious, allergic, and vasomotor rhinitis. Although they are potent agents, their prolonged topical nasal administration may result in an increase in nasal congestion following the initial decrease which occurs immediately after application. This rebound or recongestion phenomenon may lead the patient to progressively more frequent use with resultant rhinitis medicamentosa. This chronic condition, characterized by severe persistent nasal congestion, may be misdiagnosed by patient and physician as allergic rhinitis, particularly if the constricting agents were started for symptoms of allergy. Consequently, topical vasoconstrictors should be used for no more than a few days. The treatment of the rhinitis medicamentosa is accomplished by discontinuation of the sympathomimetic agent. Topical corticosteroids, such as dexamethasone nasal spray, used transiently to control symptoms until the patient's nasal mucosa returns to a normal state, provide considerable relief to these patients.

The topical effect of the alpha-receptors led to their use as oral agents for infectious, allergic, and vasomotor rhinitis. There is little evidence that these agents affect the nasal mucosa when given orally and they are not commonly used as single oral agents. They are commonly included in antihistamine-sympathomimetic combinations, some in timed release preparations. Although efficacy of such combinations over antihistamines alone is difficult to demonstrate, patient acceptance for these combinations is great, possibly owing to placebo effect or television advertising.

Oral adrenal corticosteroids in adequate doses have a dramatic effect in the control of IgE-mediated rhinitis. The mechanism by which these agents suppress symptoms is uncertain. The use of systemic corticosteroids for chronic allergic rhinitis is not appropriate therapy. The established side effects and complications of corticosteroids are such that they should not be used chronically for a disease having no mortality and only minimal to moderate morbidity. The administration of systemic corticosteroids for short periods of time such as 1 to 2 weeks during the height of a pollen season is perhaps more justifiable, but should not be an annual substitute for more appropriate long term control of recurrent seasonal disease.

A topical nasal corticosteroid, such as aerosolized dexamethasone, has significant suppressive effects on allergic rhinitis. Such therapy has less risk of corticosteroid complications because of the lower amounts administered and absorbed systemically following topical use. Intranasal use of dexamethasone is most appropriate for acute symptoms during the height of the pollen season. Long term use in chronic rhinitis is not without potential local and systemic side effects such as adrenal suppression from systemic absorption of the dexamethasone. Consequently, the standard methods of management of chronic and seasonal allergic rhinitis by other specific and nonspecific methods described above remain the treatment of choice.

Complications of IgE-Mediated Rhinitis

Although complications of seasonal allergic rhinitis are not common, chronic or perennial rhinitis is associated with complications of considerable significance to individual patients.

Allergic rhinitis may be associated with infectious diseases of the upper respiratory tract. This association is probably related to the chronic edema and resultant intermittent obstruction of eustachian tubes and sinus orifices. Acute recurrent chronic sinusitis or chronic or intermittent serous or infectious otitis media in some allergic patients may be explained in such a manner. Patients with chronic nasal allergy appear to have more respiratory infections although such a relationship is difficult to document.

The association of allergic rhinitis with nasal polyposis or asthma or both has been recognized for many years. Rhinitis might cause nasal polyps; on the other hand, the relation between rhinitis and extrinsic asthma is not considered causal but two coincidental diseases mediated completely or partially through the IgE-mediated type of hypersensitivity reaction.

VASOMOTOR RHINITIS

Vasomotor rhinitis has also been termed nonallergic or non-IgE mediated rhinitis to emphasize that it is not the result of, or related to, an immunologic reaction in the nose. If this explanation is correct, the participation of the autonomic nervous system, as has been postulated for asthma, is likely to be of importance in production of the nasal response.

Symptoms of vasomotor rhinitis include nasal congestion and rhinorrhea. There is generally less pruritus than in allergic rhinitis. Patients may note the correlation of increased symptoms with numerous nonantigenic precipitating factors such as perfumes, tobacco smoke, temperature change, and alcohol ingestion. The occurrence of symptoms following alcohol ingestion and temperature change are of value in attempting to differentiate vasomotor rhinitis from allergic rhinitis. Other differential points include the absence of associated conjunctivitis, less or absent pruritus, presence of perennial symptoms, absence of significant eosinophilia and absence of positive skin tests in vasomotor rhinitis. Familiarity with these factors greatly aids diagnosis and differentiation from allergic rhinitis. The differential diagnosis between vasomotor and allergic rhinitis may be difficult in certain patients. Such diagnostic problems include patients who have vasomotor rhinitis but coincidentally have positive skin tests to inhalant antigens unrelated to their disease. Other patients with vasomotor rhinitis may report symptoms caused by exposure to house dust which are the result of an irritant rather than an immunologic reaction. It is not rare to see such patients who have had years of injection treatment for allergy when the basic clinical problem is vasomotor rhinitis. Finally, certain patients may have both allergic and vasomotor rhinitis. Any extensive therapeutic program directed toward the management of the allergic component would be expected to alter only that aspect of the patient's problem.

Treatment of vasomotor rhinitis consists of symptomatic management as described for allergic rhinitis. An effort must be made to explain the nature of the problem, particularly the lack of relation to IgE-mediated allergic disease to the patient. Most patients enjoy such discussions and are eager to be confronted with a proper classification of their clinical problem. Patients with vasomotor rhinitis who have been misdiagnosed as allergic rhinitis and unsuccessfully treated may be relieved to learn why treatment has failed and what to expect of the future. With reassurance and symptomatic treatment many of these patients get better.

During pregnancy certain patients may be afflicted with a marked increase in nonallergic rhinitis which causes rather intense symptoms. This responds only poorly to antihistamines but generally resolves after termination of the pregnancy. In certain cases rhinitis may be potentiated by, or related to, drugs other than the rhinitis medicamentosa described above. Rauwolfia derivatives and estrogen should be considered in this regard.

RHINITIS AND NASAL POLYPOSIS

Nasal polyps are polypoid extensions of edematous nasal mucosa. They vary in size from small white projections of mucosa to huge polyps that may occlude the entire nares. Polyps sufficiently large to prolapse through the external nares or appear in the pharynx occur. The histology of the polyps shows edematous tissue with variable numbers of scattered eosinophils and neutrophils.

The symptoms produced by the polyps are dependent on their size and location. When small they may be asymptomatic and found only by examination of the nose. If they are large, they may completely occlude the nasal passages and produce significant symptoms of upper airway obstruction. Polyps occluding the sinus orifices may presumptively result in obstruction or inhibition of normal drainage of sinuses and result in retained secretions and infectious sinusitis.

The etiology of nasal polyposis is unknown. Clinical observation has demonstrated correlations between polyps and infection in the sinuses. Even with IgE-mediated rhinitis, the incidence of nasal polyps appears to be higher than in the general population. It has been recommended, in fact, that patients with nasal polyposis who have allergic rhinitis and nasal polyposis be predominantly managed by control of the allergic reaction in the nasal mucosa. Such management has been advised on the presumptive basis that recurrence of nasal polyps will be prevented by this approach. There are no conclusive data that polyps are prevented by standard allergy therapy. The patient with polyps who has marked symptoms of allergic rhinitis needs appropriate therapy for his rhinitis. In the atopic subject with minimal nasal symptoms but with recurrent nasal polyps the best course of action is not established.

In some patients, the removal of nasal polyps has been followed by the onset of asthma and conservative management rather than polypectomy has been recommended on the assumption that there is a cause and effect relationship between polypectomy and onset of asthma. Samter and Beers believe this is more than a coincidental relationship,[6a] and until further information establishes or disproves such a correlation, it must be considered by managing physicians.

If the polyps are so large that they occlude the nasal passages, surgical removal might be unavoidable. If the polyps are small, only periodic observation may be necessary. For recurrent polyps or polyps which are not extremely large, topical nasal corticosteroids are often effective in reducing their size. Thus, the judicious use of aerosolized dexamethasone may reduce the frequency of polypectomy in patients who have recurrent polyps or avoid the necessity of polypectomy in others. Trial of such a dexamethasone nasal spray (2 sprays in each nostril 3 times daily) for 2 to 3 weeks with re-examination may demonstrate a significant reduction in polyp size. The use of the dexamethasone nasal spray at this dosage *should not be continued indefinitely.* The amount of dexamethasone delivered (and possibly entirely absorbed) at this dosage is approximately 1 mg. (equivalent to 5 mg. prednisone) and, because of systemic absorption, can result in adrenal cortical suppression if continued a sufficient period of time. If the initial trial of management of the polyps by dexamethasone delivered to the nose is successful, further management may be accomplished by use of the corticosteroid *intermittently*, preferably with alternate day therapy.

A curious triad of nasal polyps, aspirin sensitivity, and asthma exists. This triad is uncommon but in a referral practice or center where large numbers of patients with asthma are seen, the problem is not rare. These patients have nasal polyps, chronic asthma of the intrinsic type which in many subjects has no relation to IgE-mediated responses and a history of a reaction to aspirin. The latter is characteristically described as the sudden onset of very severe, possibly fatal asthma within minutes of aspirin ingestion and without other manifestations of anaphylaxis. The mechanism of action of aspirin is uncertain, and the interrelationships of the polyps, chronic asthma, and aspirin reactivity are not yet understood. The patients often have sufficiently severe asthma to require chronic corticosteroid therapy, preferably on alternate days.

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The Pathogenesis of Asthma

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> Hence it may be concluded every inveterate Asthma to be a mixt affection, stirr'd up by the default partly of the Lungs ill-fram'd and partly by default of the Nerves and nervous Fibers appertaining to the breathing parts.
>
> THOMAS WILLIS, 1684

> In what then, does the peculiarity of the asthmatic essentially consist? Manifestly, in a morbid proclivity of the musculo-nervous system of his bronchial tubes to be thrown into a state of activity; the stimulus may be either immediately or remotely applied but in either case would not normally be attended by any such result. . . . The vice in asthma consists not in the production of any special irritant but in the irritability of the part irritated.
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> HENRY HYDE SALTER, 1882

Perhaps a better title for this article would be, "The Many Pathogeneses of Asthma," for there are many factors to consider. Some, especially the altered pulmonary physiology with abnormalities in ventilation and perfusion, are common to all patients. Others are factors that can provoke episodes of asthma. Each of these may be operative in some patients and not others. For proper management of an individual patient it is important to identify and understand those factors operating in his particular case.

In this article I will discuss the provocative factors that are not discussed elsewhere in this symposium, and also discuss the present status of attempts to explain asthma as a disease resulting from the operation of these factors through a final common pathway.

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ALLERGY

When allergy to inhaled antigens is a cause of asthma, the mechanism is presumably the same as the mechanism described for IgE-mediated rhinitis in Dr. Patterson's article. Questions remain. It is not clear, for instance, how particles as large as ragweed pollen can possibly reach and penetrate into the mucosa of the lower respiratory tract – this is only one of many problems which demand further study.

EXERCISE

The phenomenon of exercise-induced asthma has attracted considerable attention in the last decade. It is especially common in older children and young adults, though perhaps older adults in our mechanized society rarely exercise enough to elicit the response. To provoke asthma, the exercise must be vigorous, steady, and prolonged for 5 to 10 minutes. Bronchoconstriction does not occur during the exercise but develops after the exercise stops. Not all forms of exercise are equally effective in provoking bronchoconstriction. Free running is the most effective form of exercise, running in place on a treadmill less so, bicycling still less, and swimming hardly effective at all.[14] The mechanism of exercise-induced bronchospasm is not fully established. It may be due, in part, to the bronchoconstrictive effect of hypoxia, or of lowered carbon dioxide level from hyperventilation occurring because of the abnormal ventilation perfusion ratios characteristic of asthma, or to metabolic acidosis.[12, 41] On the other hand, other investigators have not been able to prevent bronchoconstriction by adding carbon dioxide to the inspired air, and suggest that exercise may release bronchoconstricting mediators of some kind.[31] The degree of exercise-induced bronchospasm does not seem to be correlated with rise in lactate or fall in $PaCO_2$.[46] Barboriak and co-workers[3] found that the rise in blood levels of free fatty acids after exercise was less than normal and suggested that asthmatic subjects may have to rely more on carbohydrate for an energy source.

In any case, exercise-induced bronchoconstriction can be prevented by sympathomimetics but not by atropine.[12] Cromoglycate prevents it in some subjects,[5, 37] but how it does so is unknown.

EMOTION

Physicians who treat patients with asthma are well aware that attacks often follow emotionally charged encounters. The importance of these events as provocative factors of episodes of asthma is no less for being dependent more on anecdotal validation than quantitative evidence, though attempts have been made to correlate asthma with emotional states.[21, 24] In some patients these emotionally charged encounters seem to be the main reason for episodes of asthma, but there is no characteristic premorbid asthmatic personality, and asthmatics have no more psychopathology than the general population.[1] Intensive psychotherapy is rarely indicated, but patients may benefit from the opportunity to discuss their feelings about their disease.

There are several physiologic pathways by which an emotionally meaningful stimulus could provoke bronchoconstriction. One is hyperventilation, leading to low $PaCO_2$ which in turn results in bronchoconstriction. Sudden deep inspiration also stimulates the irritant receptors of the lung and initiates reflex bronchoconstriction. Another is an alteration in hypothalamic function favoring parasympathetic (bronchoconstrictive) over sympathetic (bronchodilating) discharges.

RESPIRATORY INFECTION

Respiratory infections are among the most common events provoking episodes of asthma, especially the more severe ones requiring hospital treatment. For many years it was considered that bacterial infection was of prime importance and that the mechanism of the asthma was an allergic reaction to pathogenic bacteria or to an overgrowth of organisms of the normal flora. However, recent studies in several centers show unequivocally that the infections provoking asthma are due primarily to respiratory viruses. In infants the illness may be very difficult to distinguish from bronchiolitis.[18] In this age group the most important infectious agents are respiratory syncytial virus and parainfluenza virus.[17, 30, 49] In older children and adults, rhinoviruses and influenza virus predominate.[17, 36] In our own study we found that simple colonization of the respiratory tract by viruses is not sufficient to provoke asthma.[36] Attacks of asthma occurred only when there were symptoms of fever, malaise, cough, or coryza. Also, if it occurred at all, asthma usually began on the same day as the respiratory infection.

The mechanism of virus-induced attacks remains to be elucidated. Three possibilities are: an allergic response to the virus, decreased threshold for stimulation of the irritant receptors of the airways by the respiratory mucosal infection, and an alteration of autonomic nervous system responses of the airways. I will have more to say about these last two possibilities later.

Not only do virus infections provoke episodes of asthma, but often they seem to usher in the asthmatic state itself. The very first attack may follow closely on a respiratory infection, usually by rhinovirus, respiratory syncytial virus, myxovirus, or mycoplasma. But after the infection is over, chronic asthma may continue, and recurrent episodes of increased bronchoconstriction occur with subsequent infections by other viruses.[17] The reason for this sequence of events remains totally unexplained. In children this event occurs primarily in families with a history of asthma, hay fever, or eczema, but in older adults a family history of allergic disease is unusual. In either case asthma of this kind has a good prognosis and many patients recover after several years.

The fact of this recovery argues against genetic factors playing more of a predisposing role in the pathogenesis of infection-induced asthma.

ASPIRIN AND "ASPIRIN-LIKE" DRUGS

Aspirin provokes violent sharp acute attacks of asthma in some patients, especially those with nasal polyps and chronic asthma where inhalant allergy is not a prominent factor. Occasionally the reaction is fatal. The frequency increases with age. This type of reaction is very rare before adolescence. It may be familial.[27]

In these patients, indomethacin or mephenamic acid may cause similar alarming reactions. Sodium salicylate, acetominophen and propoxyphene do not, and can be used as substitute analgesics.[45] A few aspirin-sensitive asthmatic subjects may also react to artificial colorings (notably tartrazine yellow) added to foods, drugs or cosmetics.[8]

The mechanism of the reaction remains only partly understood. Clearly, it is not IgE-mediated allergy to aspirin or its metabolites. Presumably these patients have an idiosyncratic pharmacologic reaction to aspirin.[46]

COLD AIR, DUSTS, AND FUMES

Most, if not all, patients develop transient bronchoconstriction when they breathe cold air. Similar responses occur upon inhalation of nonallergenic ("inert") dusts and irritant chemicals such as sulfur dioxide.[50] Air pollution, especially severe air pollution after a thermal inversion, gives asthmatics special difficulty[55] and many cannot tolerate being in a room in which others are smoking.

The list of irritants that provoke asthma is very long and includes perfumes, cosmetic sprays of various kinds, household deodorizing sprays, tobacco smoke, cooking odors (especially hot grease), paints and other petroleum solvents, and many industrial dusts and fumes.

The mechanism of the bronchoconstriction from irritants has been extensively investigated by Widdicombe, Nadel, and their colleagues.* In summary, stimulation of sensory nerve endings, the irritant receptors, either in or just beneath the bronchial epithelium causes reflex bronchoconstriction. In the trachea and larger bronchi, stimulation of the irritant receptors also causes coughing. The sensory neuron travels to the medulla via the vagus. The efferent neurons responsible for bronchoconstriction are also in the vagus, and bronchoconstriction is a cholinergic reflex. The reflex can be blocked in animals by cutting or cooling the vagus and in normal and asthmatic man, as well as in animals, by ganglionic blockade with hexamethonium or cholinergic blockade with large doses of atropine.[18] Patients with asthma have two distinct abnormalities involving this reflex cholinergic bronchoconstriction. Their sensory neurons are hyperirritable and respond to concentrations of irritants too low to affect normal persons. And the extent of the bronchoconstriction greatly exceeds that ever attainable in normal persons even after maximal stimulation.

Atropine, or belladonna, has traditionally enjoyed a minor place in treatment of asthma, but doses large enough to be effective exert sufficient action on the heart, mucus and salivary glands, and eye to preclude general therapeutic use. Aerosol atropine is presently being reevaluated.

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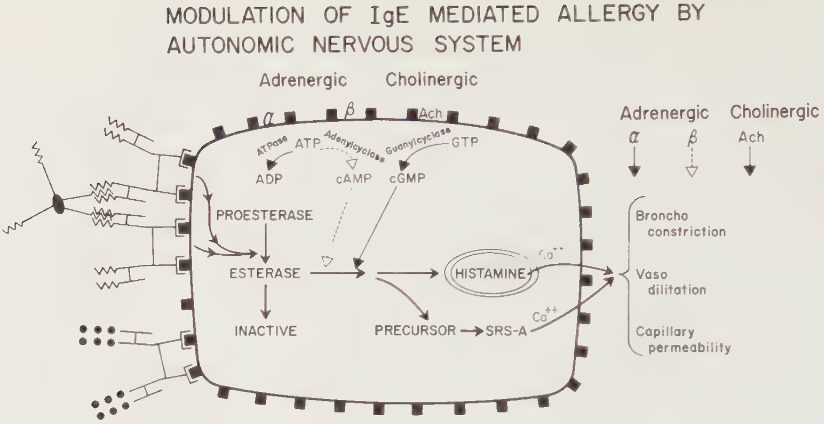
*References 10, 15, 35, 38, 47, 50, 54.

ABNORMAL AUTONOMIC RECEPTOR FUNCTION – A FINAL COMMON PATHWAY?

Because of this variety of factors that provoke asthma in different persons many students of the disease consider asthma a syndrome with many causes. Some would discard the use of the term "asthma" altogether, believing it leads to more confusion than understanding. However, in my own practice I find among my patients individuals whose attacks may be provoked by almost any conceivable combination of allergy, exercise, infection, aspirin, and irritants (as well as persistent airway obstruction and attacks that do not seem to be caused by any one of them). Many of my patients do not fit into any neat classification of "intrinsic" or "extrinsic," "infectious" or "allergic," "psychogenic" or "aspirin-induced." In my opinion asthma is a single disease with a single basic cause and each of these provocative factors acts somehow on a single common pathway. Inasmuch as all patients with asthma have a greatly increased reactivity of the airways to irritant stimuli, histamine, and acetylcholine or methacholine, this basic cause of asthma is most likely to be found by investigating the mechanism of this increased reactivity.

The airways are under the control of the autonomic nervous system. Cholinergic stimulation causes constriction, adrenergic stimulation causes dilatation. Cholinergic control of the airways is exerted via the vagus. I have already described the vagal reflex that arises from stimulation of the irritant receptors, but several points need to be added. In dogs, the bronchoconstrictive effect of histamine given by aerosol or by injection into bronchial arteries is prevented by cutting the vagus or by atropine.[15] Thus it seems likely that the bronchoconstriction produced by allergic reactions in the airways might also in part, at least, be exerted indirectly by stimulation of sensory receptors and activation of the vagal reflex. This is indeed the case. The degree of bronchoconstriction induced by antigen aerosols can be reduced both in dogs and in man by interrupting the vagal reflex.[15, 20, 53]

Adrenergic influence on the airways is exerted primarily through circulating catecholamines. Sympathetic innervation to the bronchi is sparse and directed chiefly to the cholinergic ganglia where sympathetic stimulation inhibits ganglionic transmission and relieves the bronchoconstriction produced by vagal stimulation.[6] Even though effective sympathetic innervation of the bronchial muscle is lacking, epinephrine and sympathomimetic amines are, of course, potent bronchodilators. Beta-adrenergic receptors are, therefore, obviously abundant in bronchial smooth muscle. Szentivanyi[32] proposed that the mechanism of the increased irritability of the airways is a reduced response of beta-adrenergic receptors. This is the beta-adrenergic blockade theory of asthma.



Alpha stimulation lowers levels of cAMP and enhances effect.
Beta stimulation raises levels of cAMP and inhibits effect.
Acetylcholine raises levels of cGMP and enhances effect.
Theophylline inhibits phosphodiesterase, raising cAMP and inhibits effect.
Theophylline also binds intracellular Ca^{++} and inhibits effect.

Figure 1. Control of histamine release from mast cells by the autonomic nervous system. Diagram of a mast cell. The black squares represent receptor sites for IgE molecules. When two IgE molecules are bridged by an antigen the cell is stimulated to secrete histamine and other mediators. Solid arrows indicate stimulation and open dashed arrows indicate inhibition of mediator secretion. (See references 2, 19, 22, 26, 34, 39.)

Considerable evidence of reduced beta receptor response in asthmatic patients has accumulated. The epinephrine-induced rise in blood sugar and lactate is reduced,[9, 23, 28, 33] eosinopenia is less,[43] and urinary excretion of cyclic adenosine monophosphate (cAMP) is less.[4] Several cells show reduced response to beta-adrenergic stimulation in vitro. Leukocytes, principally lymphocytes, show reduced response of adenyl cyclase to isoproterenol and the second wave of epinephrine-induced aggregation of platelets is reduced.[11, 51] Epidermis of patients with atopic eczema fails to respond normally to beta-adrenergic stimulation in vitro.[7]

The cholinergic and adrenergic abnormalities have a reciprocal relationship, and the degree of severity of the two abnormalities in a series of patients was correlated.[32] The bronchoconstrictive effect of cholinergic stimulation is prevented by adrenergic agonists. Conversely the bronchoconstrictive effect of the beta blocker, propranolol, is prevented by atropine.[16]

At the cellular level, too, there is reciprocal inhibition of beta-adrenergic and cholinergic stimulation. Beta-adrenergic stimulation leads to increased intracellular concentration of cyclic adenosine monophosphate (cAMP)[44] and cholinergic stimulation to increase of cyclic guanosine monophosphate (cGMP).[13] Although beta-adrenergic stimulation by itself has no effect on cGMP it attenuates the rise in cGMP induced by concurrent cholinergic stimulation; and vice versa, cholinergic stimulation attenuates the rise in cAMP induced by adrenergic stimulation.[25]

For these, and other reasons, I believe that the basic defect in asthma will be found in one of the complex chains of biochemical reactions at the cell membrane that are involved in this reciprocal control of the response of the cell. I think it is likely that this membrane defect involves many cells, including especially mast cells, sensory and motor neurons of the vagal reflex arc, and smooth bronchial muscle and mucus glands. In this view, the asthmatic attack results from a feedback amplification of the signal from the bronchial irritant receptor. I have discussed this hypothesis in some detail elsewhere.[12] Let me simply illustrate it by the example of allergic asthma. The antigenic release of histamine from mast cells would be increased in asthmatics because this membrane defect of the mast cell would promote secretion of histamine and other mediators (Fig. 1). The irritant receptor of the sensory neuron would be in a less polarized state and more easily stimulated. On the efferent side of the vagal reflex, ganglionic transmission would be facilitated. Finally, as at least the fourth stage of amplification the smooth muscle and mucus glands would have an exaggerated response to the cholinergic nerve stimulation. A feedback loop is established since the bronchoconstriction itself stimulates the irritant receptor of the sensory neuron. A full-blown attack would thus be produced by a relatively minor triggering stimulus.

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Skin Tests in the Diagnosis of Allergies of the Immediate Type

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It is just over 100 years since Blackley first described the allergen-induced wheal and erythema skin response as a useful diagnostic procedure in atopic patients.[2] The fact that skin testing is still in widespread use is evidence enough that it has withstood the test of time as a basic tool of the allergist. On its centennial anniversary, it seems particularly appropriate to examine once more the usefulness of the immediate wheal and erythema skin test, especially in light of the recent development of newer in vivo and in vitro diagnostic tests.

The immediate skin test reaction is due to the interaction between antigen and IgE skin-sensitizing antibody bound to tissue mast cells. The skin test procedure must deliver an appropriate amount of aqueous antigen beneath the stratum corneum and the barrier zone of the epidermis in order to combine with the tissue mast cell. The IgE molecule has a particular affinity for mast cells and basophils. The affinity is based on two inherent features. First, the Fc portion of the IgE molecule contains the structures essential for attachment to the cell sites. Second, the receptor sites of the cell are surface structures on the plasma membrane capable of binding the Fc portion of the IgE molecule. The only immunoglobulin present in significant amounts on basophils and mast cells is IgE. It is estimated that between 30,000 and 100,000 receptor sites are located on each mast cell.[10]

Two IgE molecules are required for the formation of skin-reactive complexes. One antigen molecule must bridge or combine with at least two antibody molecules on the cell to be effective in vivo. When the combination of one antigen and two antibody molecules occurs, there is an allosteric phenomenon probably involving structural changes in the IgE antibody molecule. This affects the cell membrane so as to result in the liberation from the cell of mediator substances, most notably histamine. These mediators cause local vasodilatation and increased capillary permeability resulting in the positive wheal and erythema reaction.

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It is not the purpose of this chapter to discuss the technical aspects of allergen preparation or the various skin test procedures and their advantages and disadvantages. Instead we will devote our attention to some of the common misconceptions of skin testing and the fallacies of both the positive and negative skin test.

Fallacies of the Positive Skin Test—The "False-Positive" Skin Test

Improper Preparation and Administration of the Allergen Solution.[13] Skin testing is performed with an aqueous solution of the antigen prepared by extracting the appropriate allergenic material with buffered saline. Many factors may contribute to producing a skin testing solution which is nonspecifically irritating. Deviation from a physiologic pH or proper osmolarity will cause a false-positive skin test. Many extracts, particularly foods, house dust, and feathers, contain irritants of low molecular weight and it is necessary to dialyze these materials befor utilizing them as skin testing agents. Glycerine, commonly used as a preservative in allergy extracts, will cause nonspecific irritation at a concentration of 6 per cent if injected intradermally. Injecting too large a volume of extract intradermally will also cause false-positive reactions. The optimal volume is 0.02 ml.

Substances Which Nonspecifically Release Histamine or Contain Histamine Themselves. Materials which are urticariogenic will cause a wheal and erythema skin test response in all subjects. Example are morphine and codeine. Some food extracts, particularly cheeses, have high histamine content and will cause false-positive reactions.[1]

Dermographic Subjects. It is estimated that dermographism is present in 5 to 20 per cent of the population, depending on the degree of pressure.[11] Skin testing should always include a saline control to insure that one is not dealing with a dermographic subject.

A Remnant of Past Sensitivity. It is not common to find positive skin test reactivity persisting in an individual whose clinical sensitivity has disappeared.

A Harbinger of Future Sensitivity. The onset of the clinical symptoms of allergic rhinitis is generally preceded by a positive pollen scratch test. Hagy and Settipane[7] found that the frequency of new hay fever developing in college seniors who had no clinical manifestations of allergy as freshmen is more than 10 times higher in students with initial positive pollen scratch tests than in students with no positive pollen scratch tests. Individuals with 2 plus or greater skin tests developed hay fever more than 13 times greater than negative pollen reactors. Thus, the risk of developing an allergic condition is considerably greater in individuals with a positive skin test.

Dissociation of Positive Skin Reactivity and Clinical Sensitivity. Perhaps the most important reason for the false-positive skin test is the physician's failure to realize that a positive skin test reaction is not necessarily an indicator of clinical sensitivity. IgE allergic antibody is not always fixed in both the patient's skin and the allergic shock organ. Therefore, the simple presence of a positive skin test does not insure that the allergic antibody is also fixed to the conjunctiva, the nose, or the bronchial tree.

Special mention should be made of skin tests for reactivity to foods. It is here that there is the widest discrepancy between skin reactivity and clinical sensitivity. It has been estimated that only 20 per cent of skin tests positive for certain foods have a positive clinical correlation.[9] The best correlation is found in patients who develop symptoms immediately after ingestion of a food. The correlation is much less when the onset of symptoms is delayed. The patient may show a positive skin test for the undigested food but may be nonallergic to digestive breakdown products. More will be mentioned later on the subject of the antigenic changes in foods caused by digestion.

The Fallacies of the Negative Skin Test – The "False-Negative" Skin Test

Improper Preparation and Administration of the Allergen Solution. Allergy extracts lose potency with storage. Therefore, outdated extracts will give a false-negative reaction. One has to be sure that the extraction procedure was long enough and carried out with the correct buffer to insure that the allergenic material is indeed present in the solution. In addition, the appropriate material must be used as the initial source of allergen. An example is the proper preparation of dog or cat extract. Animal hair or fur is practically devoid of soluble antigen. Therefore, extraction of dog hair clipped from the animal will contain little antigen. In order to prepare a proper allergen solution of dog, the skin or dander, which can readily be obtained by brisk brushing of the animal, must be used.

As stated earlier, the allergen solution must penetrate the stratum corneum and barrier zone of the epidermis in order to combine with the tissue mast cells. Too superficial a scratch or prick of the skin will not deliver an adequate amount of allergen solution to the mast cells.

Inherent Host Factors. The age of the subject to be tested must be considered in evaluating a negative skin test response. The skin of young infants and very elderly patients will yield smaller skin test reactions. Other host factors affecting skin test response include the temperature of the skin and the integrity of the autonomic innervation of cutaneous vessels.

The Refractory Period After an Anaphylactic Reaction. Shortly after a severe systemic reaction to an allergen, the patient may enter a refractory period because of exhaustion of the skin-sensitizing antibody, Skin testing during this period may yield a false-negative response. It is necessary to wait 2 weeks after a systemic reaction to, for example, an insect sting before one can accurately skin test an individual with stinging insect antigen.

Negative Skin Test Reactions to Food. As noted earlier, there is a poor correlation between skin test reactivity to foods and clinical sensitivity. Spies et al.[11] have recently reported studies that may explain why patients may have a negative skin test reaction to a particular food and yet have an allergic response on ingesting that food. They simulated stomach digestion by subjecting B-lactoglobulin to 6 successive 8 minute pepsin hydrolyses. These procedures resulted in the formation of 8 new antigens quite different from the original B-lactoglobulin. Therefore, a patient may be nonreactive to the original food but could respond to new antigens formed by the digestive process.

Negative Skin Test Reactions to Drugs. Many diagnostic and therapeutic agents will not elicit a positive skin test reaction although they will cause serious systemic reactions in sensitive individuals with ordinary use. Examples include local anesthetics, aspirin, and radiopaque dyes. It is imperative that the physician not be misled by a negative skin reaction in such situations. Glib administration of the agent may result in a life-threatening reaction.

Drug sensitivity may often be due to an immunogenic hapten protein conjugate formed by a metabolic product of the drug in combination with a tissue protein. Skin testing with the drug alone would obviously result in a negative reaction.

Drugs Which Inhibit the Skin Test Reaction. There is great misunderstanding about medications which inhibit immediate skin test reactivity. The error is generally in attributing inhibitory properties to agents which do not in fact possess such a property. It is, however, important to consider a negative skin test response in terms of possible inhibiting drugs.

Most authors have concluded that corticosteroids have no effect on the immediate skin test response.[5, 6] This is in contrast to the markedly inhibiting effect that it has on cell-mediated immunity or the delayed hypersensitivity tuberculin-like reaction. There is one report of triamcinolone given over a 3 day period significantly inhibiting allergen-induced skin reaction.[8]

Galant et al.[6] have demonstrated that neither ephedrine nor aminophylline given by clinically useful routes and in the usual dosage causes significant inhibition of histamine or allergen induced wheal and flare reactions. The question of the inhibitory effect of these two drugs in combination is not settled.

Subcutaneous epinephrine appears to cause a short term inhibition of the wheal and flare reaction.[12] Isoproterenol is weakly inhibitory of the allergen induced skin test by the sublingual but not by the aerosol route.[12]

Antihistamines have been known for many years to inhibit immediate skin reactivity.[1] The most potent inhibitor of this group is hydroxyzine which, given over a 24 hour period, significantly inhibits the skin test reaction for at least 24 hours after the last dose.[6] Antihistamines should be discontinued at least 24 to 48 hours before skin testing. Recent evidence indicates that there are significant individual differences in patients' ability to metabolize antihistamines.[3]

CONCLUSION

Much attention has been given in this article to the potential fallacies of skin tests in the diagnosis of allergies of the immediate type. Yet after 100 years, skin tests are still a valuable diagnostic tool for the allergist. It is essential, however, to avoid the pitfall of placing too much emphasis on either the positive or negative skin test. No test, whether in vivo or in vitro, old or newly developed, provides the final diagnosis. To hand the patient a list of inhalants and foods to which he or she is "allergic" based solely on positive skin tests is indefensible. The physician needs a thorough knowledge of his patient. Any diagnostic test, including skin testing, must be interpreted in the clinical light, in terms of the history and physical examination.

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Bronchial Inhalation Procedures in Asthmatics

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Bronchial provocation tests employing antigenic extracts, methacholine, and histamine are being increasingly used by many laboratories. The purposes for their use are many: to better understand the mechanisms of an asthmatic attack; to evaluate the degree of immunologically and nonimmunologically induced airway hyperreactivity; to assess the effects of immunotherapy on bronchial sensitivity; and in some instances as a standard by which to compare other tests such as the radioallergosorbent test (RAST) or skin test.[1, 2] Many interesting and provocative papers on this subject will by necessity not be cited in this brief evaluation of the current status of the procedure.

There is a tremendous variability in the methodology employed for skin tests and for bronchial challenge. It is usually not possible to compare results among investigators. For example, some[21, 23] used the prick test to compare their subsequent inhalation challenge whereas others used the intradermal method.[16] Another example of variability among investigators is the concentration of antigens used for inhalation challenge.[7, 9, 12, 17, 35, 45] For reasons to be discussed below, our laboratory limits the maximum concentration of antigens used to a 1:1,000 w/v.[40]

Some individuals have immediate bronchospasm following inhalation challenge which is reversed by isoproterenol but which is followed by a second drop in pulmonary function 4 to 6 hours after the initial challenge. There is considerable controversy regarding the cause and the frequency of these late reactions as discussed by Booij-noord.[3] We believe that there are at least three major considerations which are essential in designing a protocol for bronchial inhalation challenge testing to be both safe and potentially productive in yielding clinically or experimentally meaningful results. Disregard of these principles

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will invalidate or confuse the results. These considerations are as follows.

1. Patients with reversible obstructive airway disease (asthma) have hyperreactive airways and the stimulus to induce a bout of bronchospasm need not be mediated by antigen-reagin interaction, e.g., bronchospasm with exposure to noxious fumes, strong odors, or temperature changes. Indeed, asthmatics have one common denominator: they respond with bronchospasm to lower concentrations of either methacholine or histamine than nonasthmatics.

Townley, Dennis, and Itkin[15] have shown that adult asthmatics had a greater than 15 per cent decrease in forced expiratory volume in one second (FEV_1) after breathing a few breaths of a dilute solution of methacholine, whereas normal subjects had no fall in FEV_1 after 150 breaths of the same solution. Interestingly enough, subjects with hay fever were not entirely normal in that 8 of 14 persons challenged had a greater than 15 per cent decrease in FEV_1 after an average of 77 breaths.

Our own experience in testing severe perennial asthmatics with methacholine[41] indicates that with a single exception, approximately 85 per cent had a positive test, i.e., $\geqslant$ 20 per cent fall in FEV_1 following a maximum 77 breaths of 0.25 mg. per ml., and approximately 15 per cent had positive tests with a maximum of 77 breaths of 2.5 mg. per ml. Many cases of perennial severe asthmatics cannot even tolerate an inhalation challenge with saline after bronchodilator medications have been withheld for periods of between 6 and 12 hours. Thus we believe that in these individuals there is an imbalance of the autonomic nervous system controlling the caliber of their pulmonary airways. There is evidence to indicate that the mechanisms involved are: a partial beta-adrenergic blockade,[43] a hyperreactivity of the alpha-adrenergic system,[8, 39] a hyperreactive or unopposed cholinergic system,[19] or a combination of these three. The resulting condition, the so-called "twitchy lung syndrome,"[13] may be due to various combinations of the defects just listed.

2. Positive immediate intradermal skin tests may be found in asymptomatic persons when the concentration of pollen test antigen is 10,000 total nitrogen units (TNU) per ml.,[27] a dose which converts to approximately 4,000 protein nitrogen units (PNU) per ml.[38] These positive tests which were clinically insignificant were immunologically specific, since many of them could be passively transferred to nonreactive individuals. With ragweed, grass, and pollen extracts, it was found that none of the 100 control subjects responded with a positive test to a concentration of 100 TNU. These negative findings among control subjects were in contrast to the approximate 85 per cent incidence of positive skin reactions with the 100 TNU per ml. concentration of ragweed extract when tested in 66 subjects with well documented histories of rhinitis or asthma during the ragweed season.[27] It has been shown that sera of normal individuals contain IgE, albeit with an average level less than that of individuals with reagin-induced asthma.[25] These data also cast considerable doubt on the clinical significance of positive intradermal skin tests obtained with antigens more concentrated than 1:1,000 w/v, or approximately 500 PNU per ml., on a subject with perennial asthma of unknown etiology.

3. Just as the concentration of test antigens is critical to the proper evaluation of skin tests, there is evidence to indicate that high concentrations of aerosolized antigens can induce immunologically specific but clinically insignificant inhalation challenge tests. For example, inhalation of an average of 40 breaths of 10,000 PNU per ml. of allergen induced significant bronchospasm in 11 of 14 adults with hay fever who had not previously had asthma during the specific season for that antigen.[45] Clearly then, 10,000 PNU per ml. or approximately 1:50 w/v is too high a concentration to be used as a test antigen for those with perennial asthma of unknown etiology. The combination of hyperreactive airways and minimal amounts of specific reagin provides a mechanism whereby inhalation challenge with high concentrations of aerosolized antigens could induce a bout of bronchospasm in a laboratory which would not occur under natural circumstances.

It should also be noted that the use of aqueous solutions of pollen extracts has introduced a highly artificial situation which is difficult to extrapolate to the natural situation. For example, bronchospasm developed in only 4 of 8 patients who inhaled 200 to 1500 ragweed pollen grains, yet bronchospasm could be induced in the other 4 when challenged with an aqueous extract of 800 grains.[22] Further investigating this problem, Busse, Reed, and Hoehne[5] demonstrated that small antigenically active pollen fragments are present in ambient air and proposed that these fragments may be responsible for the bronchospasm which occurs under natural conditions. Similarly, Wilson et al.[47, 48] were unable to induce immediate bronchospasm following inhalation of washed technetium-labeled pollen grains, but they did observe severe bronchospasm 4 to 6 hours following the challenge. They suggested that the pollen grains were inhaled, deposited into the mouth and oral pharynx, swallowed, and significant amounts of the appropriate antigens eventually absorbed through the gastrointestinal tract and subsequently reaching the lungs via the circulation. The same proposed mechanism could be a possible explanation for bouts of bronchospasm reported 4 to 6 hours following inhalation challenge using high concentrations of aerosolized aqueous antigen.

In summary, the three considerations discussed above have led us to conclude that positive bronchial inhalation challenge tests using antigen concentrations approximating 1:50 w/v or greater can be expected to give a significant number of positive tests which are not necessarily clinically significant. Similarly, even skin tests with pollen extracts of 1:1,000 w/v or approximately 500 PNU per ml. are suspect because this concentration of ragweed pollen can elicit positive skin tests in 8 per cent of an asymptomatic population. Accordingly, we have compared skin tests with graded concentrations of antigens with a series of provocative bronchial inhalation tests.

Materials

Nonglycerinated antigens were purchased from Hollister Stier Laboratories, San Leandro, California. The same allergen preparations that were used for intradermal testing were also used for bronchial challenge. Single allergens were used for bronchial challenges in most cases. However, when mixtures were tested and a positive result ensued, the patient was retested to the single components as well. Medications were withheld prior to skin tests or bronchial challenge: 6 hours for short-acting bronchodilators, 12 hours for long-acting bronchodilators, and 24 to 48 hours for antihistamines, depending on the agent used.

The diluent used for skin testing and all bronchial inhalation procedures was phosphate-buffered saline with 0.4 per cent phenol (Hollister Stier Laboratories).

Selection of Patients

One hundred and eighty-one hospitalized patients from 14 to 70 years of age were studied. All were responsive to methacholine and histamine. Most patients had perennial asthma, though a few had seasonal symptoms. Most had severe asthma, although some with relatively mild asthma were also included.

Skin Test Techniques

Since the antigen inhalation challenges were largely dictated by the skin tests results, a description of skin test techniques is of importance.

INTRADERMAL TESTS. A 26 gauge needle is used for intradermal injections which are given in the upper arm just below the deltoid area. Serially diluted antigens are given from 10^{-5} to 10^{-3} w/v dilutions but more dilute concentrations for the initial skin tests were used when unusual histories indicated an exquisite sensitivity. Only aqueous extracts of pollens, molds, dusts, and in a few instances danders were used. Extracts more dilute than the 10^{-3} w/v concentration were diluted the same day. As close to 0.02 ml. of fluid as possible was administered. Two control solutions were given concomitantly with the antigen: (1) the diluent, and (2) histamine (base) 0.1 mg. per ml. The reactions were read after 20 minutes. The largest diameter of the wheal produced by the diluent control was subtracted from that produced by the antigen. Although our data are expressed in millimeters of wheal, the following symbols can also be utilized to designate the degree of reaction:

1 to 2 mm.	±
3 to 5 mm.	+
6 to 8 mm.	++
9 to 11 mm.	+++
12 or greater	++++

We stopped at that concentration which produced a wheal 6 mm. greater than the diluent control and considered this a positive test. The histamine injection was given not only to determine the patient's ability to react to it, but also as a check for medication that might inhibit the skin test. The 0.1 mg. per ml. dilution of histamine should always produce a wheal greater than the diluent control. Recent studies imply that ephedrine and aminophylline can be given prior to skin tests but antihistamines should be withheld from 24 to 96 hours prior to skin tests.[11, 18]

PRICK SKIN TESTS. A drop of commercially available aqueous allergens in 0.4 per cent phenol at a concentration of 1:10 or 1:20 w/v was placed on the back and the skin punctured and lifted slightly using a 26 gauge needle. An attempt was made not to draw blood. The tests were usually read at 20 minutes. If an inordinately large skin reaction appeared earlier, the antigen was wiped off with a cotton alcohol sponge. Controls included diluent and histamine as described for intradermal testing but the concentration of histamine was 1.0 mg. per ml. We arbitrarily considered a wheal 10 mm. greater than the saline control as "positive."

Procedures for Bronchial Challenge with Antigens

A baseline FEV_1 of at least 80 per cent of the average best FEV_1 was required in order to qualify for testing that day. The diluent or subsequent antigen solutions were placed in a Vaponefrin glass hand nebulizer propelled by a Bell and Gossett compressor (model LCHB) adjusted to a flow rate of 6 liters per minute. The patient would then inhale two breaths of diluent, and spirometry was performed at 1½ minutes, 5 minutes, and 10 minutes after the inhalations. He would then inhale 5 breaths of diluent, with spirometry performed at the same intervals as before. This was then repeated with 10, 20, and 40 breaths. A drop in FEV_1 of 10 per cent or greater disqualified the patient from testing with other substances. In all patients, inhalations of diluent preceded antigen inhalations, to screen them for reactivity to the diluent as well as to demonstrate their stability while pulmonary function tests were performed.

Again, when scheduled for testing with antigen, a shorter inhalation prodedure consisting of 5 breaths followed by 40 breaths of diluent was given to make sure the patient was stable that day. A greater than 10 per cent fall in FEV_1 at 10 minutes after the 40 breaths disqualified the patient for that day. If the fall was not greater than 10 per cent, the patient was first given two breaths of the antigen solution. A 20 per cent fall in FEV_1 after 10 minutes was considered a positive test. A negative test was followed by 5 breaths of the same mixture. Subsequent negative tests were followed at 10 minute intervals by 10, 20 and 40 breath challenges. Occasionally if the fall was 15 per cent to 19 per cent a 20 minute wait was observed prior to a subsequent challenge. The starting antigen concentration was determined by skin tests using the dilution of antigen required to elicit a 2+ positive intradermal test. Not more than one antigen was tested per patient in a 24 hour period. After a positive reaction, a 48 hour interval between tests is desirable in order to observe for possible late reactions.

Methacholine Inhalation

The same baseline criteria as for antigen inhalation challenge were used. If the screening tests were negative, methacholine inhalation was started: 2 breaths, 5 breaths, 10 breaths, 20 breaths, and 40 breaths, or until a drop of FEV_1 exceeded 20 per cent of the baseline FEV_1. The concentration of methacholine was 0.25 mg. per ml. followed in sequence by 2.5 mg. and 10 mg. per ml., stopping at any point where a positive test was obtained.

Histamine Inhalation Challenge

The same baseline criteria as described for antigen inhalation challenge were used. If the screening tests were negative, histamine inhalation was started: 2 breaths, 5 breaths, 10 breaths, 20 breaths, and 40 breaths or until a drop in FEV_1 exceeded 20 per cent of the baseline FEV_1. The concentration of histamine was 0.02 mg. per ml. (expressed as histamine base) followed in sequence by 0.2 mg. and 1 mg. per ml., stopping at any point where a positive test was obtained.

Results

The results of 532 inhalation tests performed in 181 hospitalized methacholine-responsive asthmatics are shown in Table 1. The more dilute the antigen concentration giving a positive skin test, defined as a wheal 6 mm. greater than the saline control, the more frequently positive the subsequent inhalation challenge. With a positive skin test of 10^{-5} w/v dilution, 61 per cent of the subsequent inhalation tests were positive. At 10^{-4}, 35 per cent, and at 10^{-3}, 27 per cent were positive. It is important to note that there were only 4 per cent positive bronchial challenges on patients with negative skin tests and hyperreactive airways.

Table 2 compares the positive intradermal skin tests at 10^{-5} w/v, 10^{-4} w/v, and 10^{-3} w/v with the subsequent inhalation challenge. Certain trends are of interest. By combining the 10^{-5}, 10^{-4}, and 10^{-3} w/v dilutions in Table 3, positive skin tests with grasses and molds tend to correlate better with the inhalation challenge than do trees, weeds and dusts, although ragweeds correlated better than the other weeds.

Table 4 shows a comparison of the prick tests with subsequent inhalation challenge. There were 243 prick tests performed simultaneously with the intracutaneous tests. Since the diameter of the wheal that gives a "*positive*" reaction is arbitrary, we compared our definition of "a wheal 10 mm. larger than the diluent control" with criteria utilized by other investigators. If a wheal 10 mm. or larger than the control is considered positive, 50 per cent of the inhalation tests that followed were positive. If a greater than 5 mm. wheal is considered positive, 35 per cent of the inhalation tests were positive; and if a wheal greater than 2 mm. with erythema of greater than 14 mm. is considered positive, 25 per cent of the cases went on to have a positive inhalation challenge. The small percentage of individuals with negative skin tests that had positive inhalation challenges confirmed the occasional occurrence of nonspecific positive inhalations with high concentrations of antigens.

Table 5 summarizes the relationship between history, skin tests, and bronchial challenge, but requires some comments. Interpretation of the

Table 1. *Comparison of Skin Tests with Inhalation Challenge*

SKIN TESTS* INTRADERMAL	INHALATION CHALLENGE TO 10^{-3} w/v		
	Positive	Negative	Per cent Positive
Pos 10^{-5} w/v dil.	33	21	61
Pos 10^{-4} w/v dil.	36	66	35
Pos 10^{-3} w/v dil.	35	96	27
Neg 10^{-3} w/v dil.	9	236	4

*Positive = diameter 6 mm. > saline control

Table 2. *Comparison of Skin Tests with Bronchial Inhalation Challenge*

SKIN INTRADERMAL SKIN TESTS Antigen	BRONCHIAL INHALATION CHALLENGE Positive	 Total	 Per cent Positive
Positive at 10^{-5} w/v*	*To 10^{-3} w/v*		
Trees	4	7	57
Grasses	8	11	73
Weeds (excluding ragweeds)	3	5	60
Ragweeds	6	8	75
Dusts	4	11	36
Molds	8	12	67
All antigens combined	33	54	61
Positive at 10^{-4} w/v	*To 10^{-3} w/v*		
Trees	1	13	8
Grasses	17	27	63
Weeds (excluding ragweeds)	2	10	20
Ragweeds	5	15	33
Dusts	5	22	23
Molds	6	15	40
All antigens combined	36	102	36
Positive at 10^{-3} w/v	*To 10^{-3} w/v*		
Trees	6	22	27
Grasses	9	25	36
Weeds (excluding ragweeds)	5	34	15
Ragweeds	1	10	10
Dusts	9	25	36
Molds	5	15	33
All antigens combined	35	131	27

*Positive = diameter 6 mm. > saline control

Table 3. *Comparison of Skin Tests with Bronchial Inhalation Challenge*

INTRADERMAL SKIN TESTS Antigen	BRONCHIAL INHALATION CHALLENGE Positive	 Total	 Per cent Positive
Total positive at 10^{-5}, 10^{-4} and 10^{-3} w/v*	*To 10^{-3} w/v*		
Trees	11	42	27
Grasses	34	63	54
Weeds (excluding ragweeds)	10	49	20
Ragweeds	12	33	36
Dusts	18	58	31
Molds	19	42	45
All antigens combined	104	287	36

*Positive = diameter 6 mm. > saline control

Table 4. *Comparison of Puncture Tests with Inhalation Challenge*

PUNCTURE TEST*	INHALATION CHALLENGE (TO 10^{-3} w/v) Positive	Negative	Per cent Positive
>9 mm.	16	16	50
>5 mm.	24	44	35
>2 mm. (with erythema > 14 mm.)	25	76	25
Negative 2 mm. or less	2	75	3

*Diameter of wheal minus diameter of saline control

history among a population of mainly perennial asthmatics who have seen multiple physicians is extremely difficult. These patients sometimes cannot differentiate actual past events from the interpretation of those events or from the results of previous skin tests by someone else. In classifying our patients, we paid particular attention to the circumstances surrounding the onset of the asthma, current precipitating events, and the presence or absence of seasonal variation. The presence or absence of allergic rhinitis was not used to classify a patient. Inhalation challenges to animal danders were not performed routinely so they were greatly underplayed in our statistics. Exacerbations in winter, often attributed to house dust allergy, were in fact usually related to infections. A history of aggravation of symptoms by dusts was usually considered a nonspecific irritative phenomenon when no other reagin-associated exacerbations were mentioned.

Some facts emerge from Table 5 which analyzes 100 consecutive patients in whom inhalation challenge was performed. With a positive history of asthma and a concordantly positive skin test, only 2 out of 27 had a negative inhalation challenge. This suggests that a reliable history together with a positive intradermal skin test using antigen concentrations not in excess of 1:1,000 w/v provides a high probability that the patient will have a positive inhalation challenge. The data in Table 5 are somewhat skewed since 6 of a total of 9 individuals with negative skin tests and positive inhalation challenges which accounted for the 4 per cent listed in Table 1 are included with these 100 patients. Actually, these 6 individuals had "borderline" skin tests and bronchial challenges. One

Table 5. *History and Skin Tests Compared to Bronchial Challenge in 100 Consecutive Patients*

HISTORY* AND SKIN TESTS**	INHALATION TESTS† Total Number	Positive	Negative
Positive history, positive skin test	27	25	2
Positive history, negative skin test	5	2	3
Negative history, positive skin test	44	17	27
Negative history, negative skin test	24	4	20

*History highly suggestive

**Intradermal Skin Tests 10^{-5} to 10^{-3} w/v dilution; Positive = wheal 6 mm. > saline control

†Up to 10^{-3} w/v dilution

also wonders if cross-reacting antigens played a role in the results. Ideally – because of our arbitrary cut-off point – these patients should have been skin-tested again and rechallenged, but were not.

The 44 patients with negative histories and positive skin tests pose a special problem. The 27 patients within this group who had negative histories of asthma and negative inhalation challenge but positive skin tests usually have allergic rhinitis. It seems likely that the maximum concentration of 1:1,000 w/v used for inhalation challenge testing is below the threshold that will induce asthma at least on first exposure in patients with allergic rhinitis; this is in keeping with the findings of Feinberg et al.[15] The 17 patients with negative histories despite positive skin tests and concordantly positive bronchial challenge may reflect our problem of inadequate historical data or forgetfulness as previously mentioned. Perhaps the best way to understand this interesting sub-group would be to withhold immunotherapy and observe the patient in order to ascertain if there is an exacerbation of symptoms during the subsequent season implicated by the positive skin and bronchial challenge tests.

GENERAL COMMENTS

Other investigators who have found positive bronchial challenges with negative skin tests or found a significant number of late reactions used very high antigen concentrations.[1, 7, 12, 37, 42] Like other investigators, we also observed a few patients with a negative test and positive inhalation challenges. Unlike these investigators, we found very few instances of late reactions, but our population includes many severe asthmatics on corticosteroids, and prednisone is known to prevent the late reaction.[1, 6] Also, severe asthmatics often vary throughout the day and make assessment of a "late" reaction difficult. Since patients with positive immediate tests often receive bronchodilators, it should be remembered that Citron[6, 7] did not find that isoproterenol blocked any late reactions in his series following large doses of antigens.

In our experience, those individuals who could be tested on at least two different occasions showed similar reactivity to the same antigen ± one log. These results are similar to those found by Rosenthal et al.[36] who challenged individuals on 4 consecutive days and found no change greater than one log in their response. Since there might be a log difference in response, the first positive inhalation challenge may be positive near the maximum concentration used (10^{-3}) and a subsequent test could conceivably "become negative" at that concentration. We feel it is unwise to continue to the next most concentrated solution in view of the potential risk of causing a severe and prolonged reaction.[40]

There is some debate as to the most appropriate procedure that should be used as a pulmonary function measurement for a positive end point. Colldahl[9] first advocated auscultation, i.e., listening for rough breathing, and later thought a combination of this plus airway resistance (R_a) was most appropriate. Nilsson[33] also advocated the use of auscultation. Other pulmonary function tests such as the MMEF[26] closing volume determinations[31] or frequency dependence of compliance measurements[49] may be more sensitive for certain purposes and in some situations than an FEV_1 determination. Yet any single determination may have its own limitation, such as less availability, difficulty in performing or calculating, or even lack of adaptability to certain asthmatics. Throughout our studies we have utilized the FEV_1 and found it reproducible, speedy, and accurate, especially with repetitive measurements. Although a minimal effort is required, it did not seem to overly tax the patient. Also, in an unpublished study[28] the FEV_1 was least affected by psychological parameters compared to R_a measurements, for example. In another study, however, we found a rare individual who, despite a normal FEV_1, normal VC, and normal blood gases, had an R_a of up to 14 cm. H_2O per liter per sec. during episodes of "tightness."[11] Thus, although the FEV_1 may not be the most sensitive indicator of bronchoconstriction, in our hands it was sensitive enough to indicate an appropriate end point in most instances. Also, we are presently performing other procedures simultaneously which will be evaluated in the future, but for the reasons mentioned above will continue to use the FEV_1 as one of the indicators of a positive response.

Herxheimer[20] and Tiffeneau[44] believe that hyposensitization by inhalation can occur. Our technique of beginning with a dilute antigen concentration and progressing to more concentrated extracts until a positive test is obtained would theoretically be an ideal way of obtaining hyposensitization. We have not tried to pursue this technique.

A more worrisome phenomenon that has been described is that of hypersensitization.[20] A repeat challenge to the same antigen at a later time might require less antigen to give a positive response, and reminds us the "priming effect" described by Connell.[10] We believe that our method of increasing concentrations makes hypersensitization unlikely; we have not observed it.

Comments on Methacholine and Histamine Inhalations

Methacholine, similar to acetylcholine but with a longer duration of action, has been used as a diagnostic tool. In patients in whom the diagnosis of asthma or reversible obstructive airway disease is suspected but not proved, it can serve a very useful function. A positive methacholine test at a time when the patient is asymptomatic is highly suggestive that he has reversible obstructive airway disease and, conversely, a negative methacholine or histamine test should alert the physician to suspect other disease states. Although methacholine may be slightly more consistent in predicting the asthmatic state than a histamine challenge, recently we have found comparable bronchoconstrictive effects to serially diluted methacholine and serially diluted histamine. Certain individuals, however, are outstanding in the disparity between the effects of these two agents. In fact, we have found a severe asthmatic who could tolerate 10 breaths of 25 mg. per ml. methacholine, a negative test, yet had a positive histamine challenge with 10 breaths of 0.5 mg. of histamine base per ml. We have also studied other individuals who had improved pulmonary function tests when challenged with increasing doses of histamine instead of developing bronchoconstriction as is usually observed. Finally, we are currently investigating the possibility that the variable reactivity of different individuals to inhalations of graded concentrations of methacholine and histamine may have some predictive value with regards to the ultimate ease or difficulty in controlling their bronchospasm.

CHANGES IN BRONCHIAL CHALLENGE METHODS

Over the last year we have modified the previously described methods for the following reasons:

1. The amount of solution inhaled per breath by some individuals was not the same when two breaths of a two breath test were inhaled compared to two breaths of a ten breath test.
2. Some patients tired when 40 breaths of solution were inhaled, thereby taking in less solution.
3. It is cumbersome to express data when two parameters, i.e., concentration and dose (or number of breaths), are varied at the same time.
4. By holding the number of breaths constant and varying only the concentration of the test substance, a convenient dose-response curve can be established.

With the previous points in mind, the following modifications were instituted.

Antigen Inhalation Challenge

We use the same criteria for selection, baselines and controls which we have previously described, but only 10 breaths of diluent are given. The inhalation should be administered close to tidal volume ±50 cc. Medication should be withheld prior to challenge: 6 hours for beta stimulators, 12 hours for phosphodiesterase inhibitors, 24 to 48 hours for cromolyn sodium, 24 to 96 hours for antihistamines. The 10 breaths of the following serial dilutions are given: 1:1,000,000, 1:100,000, 1:50,000, 1:10,000, 1:5,000, 1:1,000 and 1:500. The time at which the initial antigen is given is recorded. If less than a 20 per cent fall in FEV_1 is obtained after a 10 minute wait, the next higher concentration is given. If suspicious, or if the fall is 15 per cent to 19 per cent, a 20 minute wait (10 minutes + 10 minutes) is observed. The time of the final FEV_1 after inhalation of the most concentrated antigen tested (positive or negative) is recorded. When approaching the end point, less than 10 breaths may be given to be more cautious. For a test to be positive, a 10 minute drop should be sustained for 20 minutes. Data are expressed, for example as 28 per cent/5 breaths/1:50,000/60 minutes, the latter indicating the total time required for the test and hence an approximation of the rate at which the accumulated dose of antigen had been delivered. The patients should be observed as long as feasible for late reactions. Another antigen challenge may be given 24 hours later at the earliest.

Methacholine Inhalation Challenge

Using the same criteria for adequate baseline as for antigen inhalation challenge, *10 breaths* of the diluent is given and FEV_1 is measured at 1½ and 5 minutes after. If the fall in FEV_1 is less than 10 per cent after 5 minutes, *10 breaths* of two-fold serial dilutions of methacholine are given during normal breathing beginning with 0.15 mg. per ml. and progressing to a maximum of 25 mg. per ml. Measurements of FEV_1 are again taken at 1½ minutes and a positive test should have a sustained fall of greater than 20 per cent at the 5 minute reading. A negative test is followed by 10 breaths of the next concentration. There should be a 2 hour wait and the FEV_1 should be back to baseline without the use of bronchodilators between methacholine challenge and another procedure. Timing of the test is similar to the procedure outlined for antigen inhalation and data are expressed, for example, as 28 per cent 10 breaths/0.15 mg./40 minutes.

Histamine Inhalation Challenge

Using the same criteria for adequate baseline as described for antigen inhalation challenge, 10 breaths of the diluent is given and FEV_1 is measured *immediately* and 5 minutes after. If the fall in FEV_1 is less than 10 per cent after 5 minutes, 10 breaths of two-fold serial dilutions of histamine from .06 mg. per ml. to 10 mg. per ml. histamine base are given during normal breathing. Measurements of FEV_1 are again taken immediately and a test is considered positive if a greater than 20 per cent fall is sustained for 5 minutes. There should be a two hour wait and the FEV_1 should be back to baseline without the use of bronchodilators between histamine challenge and another procedure. Timing of the test is similar to the procedures outlined for antigen inhalation and data are expressed, for example, as 28 per cent/10 breaths/0.06 mg./ml./40 minutes.

CONCLUSIONS

The use of bronchial provocation tests with antigens is expanding in the United States. It is hoped by those who use it that it will prove to be a more direct and accurate method to demonstrate the causative roles of specific aero-allergens in asthma. It now appears that skin tests do not always predict bronchial reactivity, even when graded concentrations of antigens are used for both tests. Skin tests do not provide a measure of the degree of hyperreactivity of the airways; there is no evidence to indicate that the numbers of mast cells in the skin quantitatively reflect the numbers of mast cells in the respiratory tract. In fact, there is evidence that there can be dissociation between the reactivity of skin or respiratory mast cells and the reactivity of basophils in the blood. For example, it has been shown that peripheral basophils can become unresponsive to antigen challenge without concomitant changes in skin reactivity, bronchial reactivity, or symptoms.[32] Also, serum levels of IgE may or may not reflect accurately the amount of IgE fixed to mast cells. Obviously, symptoms depend on more than the quantity of circulating IgE as determined by a RAST or any other single test.

Despite these problems, we feel that bronchial provocation procedures for antigens, methacholine, and histamine, combined with skin tests and history, provide a more adequate evaluation of reagin-mediated airway reactivity in a given patient. It might also facilitate the evaluation of immunotherapy. Although some studies already show or imply that immunotherapy can change bronchial reactivity,[24, 29, 30, 34, 46] more studies are needed using stringent criteria for a positive skin test, a positive bronchial test, and a positive history. Is should then be possible to subclassify patients (Table 5) more effectively and to establish whether immunotherapy can alter the clinical course and subsequent bronchial testing of these patients.

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Some of the changes in the bronchial challenge protocols now used in our laboratory have been influenced by a subcommittee of the Allergy Disease Centers which has held meetings to standardize bronchial inhalation challenge techniques. We are grateful for this assistance and plan to adopt our final methodology according to this subcommittee's final report.

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In Vitro Methods in Allergy

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In vitro methods in allergy have had very limited use over the years because the *in vitro* methods did not seem to relate to disease in humans. Although some animals may develop allergies, it was found impossible to develop satisfactory animal models for human allergy. Consequently, research was largely limited to studies in man.

The discovery that the peripheral leukocytes of allergic humans liberate histamine in the presence of the offending allergens opened new approaches to the *in vitro* study of human allergy.[14] The association of the allergic state with the presence of a specific serum immunoglobulin, IgE, presented new opportunities for the *in vitro* study of allergy. Largely through the work of Ishizaka, it has now been established that IgE is identical to the serum component usually referred to as reagin; this work has recently been reviewed.[10, 19]

Although it is now possible to carry out *in vitro* tests of many types, it is still necessary to correlate all such tests with tests carried out in allergic and non-allergic humans in order to permit satisfactory interpretation.

Only a few in vivo tests have been found useful for comparison with *in vitro* tests.

The most widely used is the skin test. The Prausnitz-Küstner (P-K) test, a passive transfer version of the skin test, has had very limited use as a means of evaluating *in vitro* tests. In this test, serum from an allergic individual is used to sensitize skin sites in a normal individual. A wheal and erythema will result when a sensitized skin site is challenged by the injection of an allergen. The direct test, in which an allergen is injected intradermally or administered by the scratch or prick technique, has had wide application since it is relatively easy to perform, and is one of the few *in vivo* tests that can be quantitated.

There has been much controversy over the reproducibility[2, 6, 53] and interpretation of skin tests; these are covered in a separate article. Unless end-points are determined, it is difficult to interpret skin-test results because the dose-response curve is flat, which means that over a range of concentrations between 100- and 1000-fold, the size of the skin reaction changes by small increments; a marked change in slope occurs only at the end-point.[9, 17, 42]

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Other *in vivo* tests that are employed as measures of the allergic state are provocation tests. These include nasal, bronchial, and conjunctival challenge. Spector and Farr describe elsewhere in this symposium some of the difficulties in quantitating inhalation techniques[11, 52] and suggest modifications by which these difficulties can be overcome.

DIAGNOSTIC TESTS

Total IgE

Since immunoglobulin E is associated with atopy, many investigators carried out analyses of circulating IgE in an attempt to determine whether its serum titer could be correlated with the "allergic state," and hence be used as a diagnostic tool. Although there are nonatopic conditions in which IgE is markedly elevated, such as parasitic infections or a rare myeloma, history and clinical course of these diseases would make it unlikely that they would be confused with atopic illness.

The concentration of IgE can be expressed as weight, based on the use of a purified IgE isolated from the serum of a myeloma patient, or as units. The unit is that amount of IgE contained in 0.009284 mg. of a freeze-dried serum pool.[51] The unit has been assayed in terms of myeloma IgE and found to be equivalent to 2.35 ng.[57] or 2.42 ng.[8] of IgE. It has also been shown that myeloma IgE is not significantly different from serum IgE.[15, 29]

"Normal" persons have circulating IgE. In fact, the concentration of IgE shows a remarkable range for a normal serum component. In nonatopic individuals it varies in concentration from 1 ng. to more than 8000 ng. per ml. The results in atopic individuals may range from 25 ng. to as high as 29,000 mg. per ml.[4, 5, 18, 22, 23, 27, 28, 54] The values tend to be very high in severe atopic eczema.[18, 22] Values are also high in pulmonary allergic aspergillosis, but normal in Farmer's lung.[45]

A general review of all of the data indicates that while the mean serum IgE level of atopic individuals tends to be higher than that of nonatopic individuals, there is so much overlap with values observed in the serum of those who are not atopic that a conclusive diagnosis of allergy in an individual patient cannot be made on the basis of serum IgE concentration. One group of authors has concluded that "knowledge of serum IgE level in patients seen in an allergy practice is of considerable interest, but is not helpful in a directly practical manner."[27]

Specific IgE

RADIOIMMUNOASSAY. Since total serum IgE content has only limited usefulness as a measure of the atopic state, work has been done to determine whether antigen-specific IgE content of serum would correlate better than total serum IgE with the allergic disease under study. In this type of test, the concentration of IgE with specificity for a specific allergen is measured. The method most widely used to measure specific

IgE is a radioimmunoassay known as the radioallergosorbent test, or RAST.[56] The test is carried out by coupling, through chemical means, an allergen to a cellulose support, resulting in an insoluble allergen-cellulose complex. This complex, when added to the serum of a patient, will bind antibodies specific for the allergen. To the washed antigen-antibody-cellulose complex is added anti-IgE serum labeled with radioactive iodine (either ^{125}I or ^{131}I). This radiolabeled anti-IgE will bind to the complex and the amount of radioactivity in the complex will be a measure of the IgE content of the complex. Thus, the amount of IgE in the patient's serum that is specific for any allergen coupled to the cellulose can be measured.

One of the first studies of the scope of this technique for the diagnosis of allergy used a variety of allergens coupled to cellulose; these included dog, cat, horse, and cow dander extracts; birch, timothy, and dandelion pollen extracts, and house dust extract.[11] The patients were studied by history and bronchial and rhinoconjunctival provocation tests, and were skin tested by the prick method. The overall correlation between RAST and other tests was 74 per cent, but in the most sensitive patients it was closer to 100 per cent. Others have shown similar results for extract of *Dermatophagoides farinae* (house dust mite),[52] the cod allergen,[20] and ragweed.[18, 43] One study[1] found that the correlation between RAST and other tests varied with the allergen. Thus, for cod allergy, a purified cod allergen coupled to the cellulose yielded a correlation of 93 per cent, while the house dust allergen gave a correlation of only 59 per cent.

Use of the RAST has produced various other pieces of information, such as the increase in specific IgE during the hayfever season[12, 58] and the production of specific IgE resulting from injection of allergens.[36] In the latter study the quantity of specific IgE produced in non-allergic individuals was so low that symptoms of allergy did not appear when the individuals were challenged.

The development of the RAST has added a tool that has a potential for aiding in diagnosis. It has not yet progressed, however, to a stage where serum can be drawn, sent to a laboratory, and a clinically useful diagnosis returned for each patient.

The assessment of the test by some of its developers still stands. They found that "for allergens usually resulting in obvious immediate reactions, and which give rather convincing case histories, a combination of case history and skin testing proved superior to RAST, but when the case histories were less suggestive, RAST was shown to be the superior method."[1]

One of the major problems of the RAST method may well be the quality of the extract coupled to the cellulose. Until properly standardized extracts are available, the test will have problems. That this may be one of the major problems is suggested by the fact that correlations were very high when a highly purified allergen, cod allergen, was used, but low when an extract difficult to characterize, house dust extract, was coupled to the cellulose.[1] Furthermore, most of the data have been accumulated with only a few allergens. Much more data with many allergens are needed before the test can be taken from the research laboratory and be used as a general diagnostic tool.

Rat Mast Cell Degranulation (RMCD) Test. This test attempts to measure specific IgE in the serum of allergic individuals indirectly. It is based on the assumption IgE from human serum will fix to rat peritoneal mast cells, and that in the presence of allergen the sensitized cells will degranulate as determined by microscopic observation of the cells. The test has been used thus far by very few workers, and would appear to need more development before it can be used generally.[46–49] One group of workers[50] carried out a direct test of the ability of human IgE to fix to rat mast cells and was unable to confirm that any of this human immunoglobulin has this capability.

Histamine Release

Although histamine release was long considered to be a component of "immediate" allergic reactions, it was not until 1941 that it was shown that the peripheral blood of allergic individuals liberates histamine in the presence of a specific allergen, ragweed.[30] Subsequent studies showed that ragweed[34, 39, 40, 55] and many other allergens, including foods, mold, danders, and other pollen extracts, did the same.[40, 55] It has also been reported that some individuals who had negative skin tests could liberate histamine from their blood upon stimulation with an allergen;[40] there was no explanation for these findings.

The procedure as originally described[30] involved the direct release of histamine from the peripheral blood leukocytes. Subsequent studies showed that peripheral leukocytes of non-allergic individuals could be sensitized with serum from allergic individuals, and would, after sensitization, liberate histamine in the presence of an allergen. Strangely, only 20 per cent of non-allergic individuals have cells that will liberate significant quantities of histamine when used in this test.[32] Recently, a micromethod has been described and may facilitate more extensive testing.[33]

The histamine release test, both direct and indirect, has been used for the diagnosis of allergies with variable success. It has been claimed to be useful in the diagnosis of food allergy;[40] this has been disputed.[37] In studies of allergy to algae, using a Chlorella antigen, a high correlation between histamine release and skin test response was found.[13] The test was also used to study the relationship between reactivity to mite extract (*D. farinae*) and house dust allergy.[31] It was concluded from the use of this test that the mite was not the only house dust allergen in the Baltimore, Maryland, area. The test has also been applied as a quantitative measure of blocking antibody which inhibits histamine release from sensitive cells by allergen.[41, 42]

Another version of this test is the passive sensitization of chopped monkey lung[25, 35] or human lung[38] with serum from an allergic human and to measure the histamine released from these preparations in the presence of allergen.

Lymphocyte Transformation

The ability of cultured lymphocytes of a sensitive individual to be transformed into "blastoid" cells after exposure to an antigen has been thought to reflect cellular immunity only, but it appears to occur in the presence of immediate hypersensitivities as well. The change of lymphocytes to "blastoid" cells can be determined either by direct observation of stained smears, or by the addition of tritiated thymidine to the lymphocyte cultures. The test measures the amount of tritium taken up by the cells during proliferation. The subject has been reviewed.[14]

It is difficult to assess the value of the method; comparatively few studies have been reported. It was shown to be positive in individuals allergic to ragweed, alternaria, and penicillin.[21] In a study of allergy to a number of drugs it was considered to be very valuable as a diagnostic tool, regardless of whether the allergy was immediate or delayed.[26] However, in food allergy, it does not correlate with the allergic symptoms.[37]

ALLERGEN STANDARDIZATION

One of the major problems facing allergists is the lack of extracts with known and uniform characteristics. The methods currently employed for "standardization" do not really measure the content of active allergenic ingredients: they provide rather nonspecific information such as weight to volume, or protein nitrogen units. These so-called measures of potency sometimes correlate with allergenic activity, but often do not. Furthermore, the label does not change with time or varying environmental conditions to which the extract may be subjected, but potency may be markedly altered.[3]

Failure to have extracts with uniform composition and potency may well be responsible for the variable results of *in vitro* methods used for the diagnosis of allergy. It also complicates the development of useful *in vivo* diagnostic procedures and creates problems for the proper use of extracts in therapy. Standardization of extracts, would, therefore, be a major advance for allergy. To accomplish this, *in vivo* methods are extremely valuable,[2] since they measure activity of an extract in sensitive humans. It is difficult, however, to set up standards and compare the potency of extracts in different laboratories unless *in vitro* methods are employed. The data available on standardization of extracts by *in vitro* procedures are very meager.

If an important allergenic component of an extract can be isolated, it may serve as a reference against which extracts may be standardized in a manner that predicts their *in vivo* activity. This has been accomplished for short ragweed pollen extract[6] which uses antigen E as a reference. It has been demonstrated that commercial extracts whose claimed antigen E was almost identical had up to a 500-fold variation in potency. The variation pertained not only to the antigen E content, but also to the skin reactivity and ability to release histamine from peripheral leucocytes. Similar results have been obtained with a comparatively pure rye group I allergen isolated from rye grass pollen, compared with extracts of 6 different grass pollens which share the same antigenic component.[7] Although effective for standardization of extracts, standardization will proceed slowly because of the complex and difficult problem of identifying and isolating in pure form the allergenically active component from each allergen source. An approach that holds promise is the use of radioallergosorbent test (RAST).[16, 24, 57] In a recent study the RAST was used to measure the potency of short ragweed extracts,[24] and a high correlation between skin test activity, RAST, and antigen E content was found. This study also demonstrated that among 11 commercially prepared extracts with approximately equivalent labeled potency, there was a 1000-fold variation in activity. Thus, the wide variability among commercially prepared extracts was demonstrated again.

Until uniformly potent and stable extracts become available, diagnosis and treatment in allergy might remain inexact; and many reported experimental results and conclusions might require re-evaluation.

SUMMARY

In recent years there has been an enormous advance in our knowledge of the mechanism of allergy. Especially noteworthy is the role of a specific immunoglobulin, IgE, and of leukocytes. In vitro tests have been developed, based on these findings. Results have clearly demonstrated that in vitro tests will be significant adjuncts to the diagnosis of allergy and in standardizing allergenic extracts. The tests, however, are still in the developmental stage and are not yet ready for wide routine use.

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Pulmonary Function Tests in Asthma

Are They Worth It?

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In considering which measures of pulmonary function should be carried out in the patient with bronchial asthma, one's attention turns first to airway resistance: it is almost always increased. Nervous and other mechanisms may be involved in the production of the bronchoconstriction seen in asthma. The smooth muscles of the trachea and the bronchi are innervated by vagal and sympathetic nerves from pulmonary plexuses; from here the nerves enter the lungs and form extrachondrial and subchondrial plexuses. These plexuses are united in bronchioles, where there is no cartilage. All plexuses contain ganglion cells, from which originate the parasympathetic postganglionic fibers.

Except that there undoubtedly is a great complexity and flexibility in local and central reflex control of the smooth muscles of the airways, little is known about the role of the bronchial ganglion cells. There is little quantitative data on preganglionic inflow and postganglionic outflow. Knowledge about the ganglia transmitting local reflexes is lacking, as well. The vagal fiber impulses constrict bronchial muscle, thus decreasing airway diameter and increasing airway resistance. Some data on bronchodilator response elicited by stimulation of vagal rootlets close to the medulla are available, but it is not known if this dilator action somehow supplements the effect of sympathetic fibers, or if it is different. Electrical stimulation of sympathetic fibers causes bronchodilation if the tone of bronchial muscle has been previously increased by eserine or pilocarpine.

The central nervous system origins of bronchoconstrictor and bronchodilator fibers are not known. From the facts that vagal and glossopharyngeal reflexes influence the airways, and the constrictor pathway to the airways is also vagal, it is inferred that constrictor fibers have their origin in the medulla, like other vagal efferents. Thus cortical connections must be considered in bronchoconstriction associated with suggestion or psychologic upsets, or that caused by direct electrical stimulation of brain cortex.

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Because vagal reflex changes of airway diameter persist in decerebrate cats, some degree of bronchial muscle control must come from below the hypothalamus. At the medullary level, a certain amount of bronchomotor activity is related to discharge at the respiratory center. Asphyxia and hypercapnia reflexly increase airway resistance. In animals this effect can be prevented by atropine or vagotomy. However, recordings of central efferent activity, an increase in airway resistance after a rise in carbon dioxide tension in blood perfusing the brain, and proof that carotid bodies do not take part in hypercapnic bronchoconstriction all support the central action of carbon dioxide. The effect of hypoxemia on the other hand, which also reflexly increases bronchoconstriction, is mediated by the carotid chemoreceptors. Inflation of the lungs also increases the diameter of the airways reflexly (in addition to physical factors such as increased radial traction on the bronchi); vagotomy abolishes this effect.

Of great interest is reflex response of the airways to local irritation of respiratory tract. Thus inhalation of inert dusts or charcoal as aerosols increases airway resistance by 81 per cent, as measured by plethysmography, and increases residual volume by 14 per cent. Cigarette smoke, sulphur dioxide, and cold air all increase airway resistance, as well. These effects can be blocked by atropine.

It would be important, therefore, in considering the ideal pulmonary function studies, to test the neurophysiologic aspects of centrally caused bronchoconstriction, and to determine what goes wrong in an overshooting vagal reaction to inhaled dust. The ideal testing procedure would be aimed at a subtle, very important function giving quantitative unequivocal information; and naturally, because we deal with sick people, it would have to be noninvasive, of short duration, and inexpensive. At present this goal is elusive, and we do not what we ideally should, but what we can.

PULMONARY FUNCTION TESTS

Static Pulmonary Volumes

Measurement of static pulmonary volumes is usually the first part of a pulmonary function testing session. The reasons are partly technical—the simplicity of the apparatus, methods, and calculations—and partly traditional—the determination of vital capacity was the first quantitative measurement in respiratory physiology. Hutchinson, when he introduced his spirometer in 1846, and started collecting data on more than two thousand subjects, entertained high hopes as to the diagnostic importance of his new tool. Let us do the same in 6 selected subjects (Fig. 1). The first subject is what we call a normal man: a male of average stature, between 20 and 26 years of age, and clinically healthy: his measurements will serve as a somewhat arbitrary standard. Next, we consider 3 patients with a diagnosis of bronchial asthma, 1 patient with a diagnosis of pulmonary emphysema, and finally 1 patient with long-standing pulmonary tuberculosis. Results show that the asthmatic patient might have

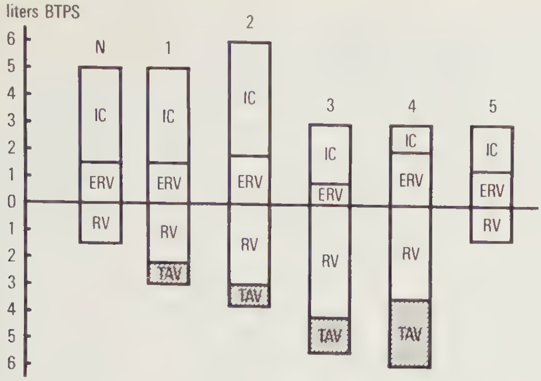

Figure 1. Vital capacity, inspiratory capacity (IC), expiratory reserve volume (ERV), residual volume (RV), and trapped air volume (TAV), as measured by spirometry, helium dilution, and body plethysmography, in 6 subjects of the same sex, age, and height. N, normal; 1, 2, and 3, patients with bronchial asthma; 4, patient with pulmonary emphysema; 5, patient with pulmonary tuberculosis. Magnitudes of vital capacity in liters are on the ordinate. BTPS: volume of gas at body temperature, at ambient barometric pressure, saturated with water vapor at body temperature. The volume measured, after expiration, in the spirometer is somewhat smaller. Upon transition to spirometer temperature, the gas is cooled and some water vapor condensed; both processes lead to volume shrinkage. Given barometer pressure, spirometer and body temperature, the original volume that was inside the lung can be recalculated. This is the volume we are really interested in, because it is related to important features in lung physiology, e.g. the position of the thorax, stretch of respiratory muscles, load upon the nonelastic and elastic components, and intrapleural pressure. Inspiratory capacity is determined from a spirometric tracing as the difference between the end of quiet expiration and the end of maximal inspiration. Similarly, expiratory reserve volume is the difference between the end of quiet expiration and the end of maximal expiration. The end of quiet expiration, the so called resting respiratory position (RRP), is taken as a reference point because at this moment in the respiratory cycle, the forces that inflate the thorax and the forces that deflate it are balanced. Among the inflationary forces are the elasticity of the thoracic skeleton, the pull of the inspiratory muscles and of the musculi erectores spinae, and the weight of the abdominal viscera on the diaphragm. Among the deflationary forces are the elastic forces of the lungs, the pull of the expiratory muscles, and the weight of the thorax and its contents. To emphasize the fact that RV cannot be determined by direct spirometry, it is shown below the zero line on an inverted scale. The helium dilution method is used to determine the functional residual capacity (FRC), i.e., the sum of expiratory reserve volume and residual volume: FRC = ERV + RV. Residual volume is then calculated as functional residual capacity minus expiratory reserve volume: RV = FRC = ERV. In young normal subjects it is approximately of same size as ERV, i.e., about 25 per cent of the total lung capacity (TLC = IC + ERV + RV). This is the complete diagram of pulmonary volumes and capacities as measured by spirometry, helium dilution and body plethysmography. For explanation of effects of various pathological conditions, see text.

a normal, better than normal, or worse than normal vital capacity, and that in the patients with emphysema and tuberculosis the vital capacity is worse than normal.

By means of a recording spirometer, the components of vital capacity can be determined. Our asthmatic patient, No. 1, does not differ from normal; No. 2 has an increased expiratory reserve volume but proportionally increased inspiratory capacity and looks like any normal athletic person—a finding quite common in young asthmatics between attacks; No. 3 has a small expiratory reserve volume but because of smaller vital capacity his inspiratory capacity is also smaller and his resting respiratory position shifted in proportion. Similar but more pronounced finding in the patients with emphysema and tuberculosis can be puzzling: What mechanisms limiting the inspiratory capacity might be common to diseases so different? Could a more detailed investigation into the air content of the thorax help? Determination of residual volume – the air remaining in the lung even after a forced expiration – by helium dilution in a closed circuit reveals this. Asthmatic patients have an increased residual volume and therefore a more or less increased total lung capacity; there is some shift of resting respiratory position into inspirium when compared to normal. Very obviously their lungs are filled with more air than they should be.

Especially interesting is the observation in the asthmatic patient No. 3 and the patient with emphysema (No. 4): their total lung capacity is markedly increased, especially in emphysema, and their small vital capacity is due to the thoracic structures approaching the stretch limits. Here the small vital capacity is caused by a primarily obstructive disease with overfilled chest; on the other hand, small vital capacity in patient No. 5 is caused by a restrictive disease, as borne out by the small total lung capacity. The detailed analysis of static pulmonary volumes can reveal individual differences between patients suffering from the same disease; and it may explain the different pathogenesis of data found falsely identical by simpler methods.

Let us assume the existence in some patients of obstructions which allow only pressure equalization and very slow gas exchange (so there will be no atelectasis) but no measurable helium penetration – *at least not during the limited duration of the test.* Then the alveolar spaces behind the obstruction would be inaccessible to helium, would not contribute to its dilution and would therefore not be measured. They could in fact be called trapped air volume. It is understood that such trapped air volume can increase, decrease, or completely disappear, depending upon the extent of of the obstruction (Fig. 2). This concept of the trapped air volume can explain why the simultaneous determination of residual volume by helium dilution and body plethysmography in some patients

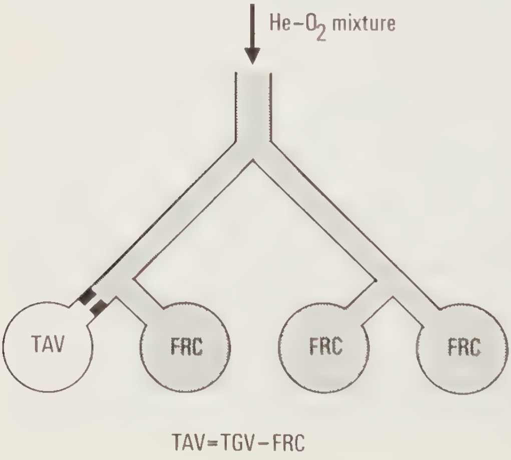

Figure 2. Concept of the trapped air volume. The helium-oxygen mixture used for functional residual capacity determination consists of approximately 10 per cent helium, 21 per cent oxygen, and the rest nitrogen. FRC, functional residual capacity; TAV, trapped air volume behind a bronchial obstruction (black sleeve). Pressure equalization but not measurable gas exchange is possible through the obstruction. Trapped air volume (TAV) is the difference between the thoracic gas volume (TGV) as determined by the body plethysmograph, and functional residual capacity (FRC) as determined by helium dilution.

gives different results, the plethysmographic figure being higher. Both methods agree within statistical limits in normal subjects. Body plethysmography measures the total content on gas in the thorax; even the spaces not communicating with the airways are measured (provided there is a pressure/volume change transmission through elastic or pliable boundaries). Helium dilution determines gas content only in those spaces where helium mixture can penetrate. The difference between these two data is the trapped air volume.

Figure 1 shows the results in our group of patients: no trapped air volume in the normal subject and in the restricted lung of the patient with tuberculosis, and measurable trapped air volumes of different sizes in the obstructed lungs of the patients with asthma and emphysema.

There are two interesting points here. First, the presence of a trapped air volume in many asthmatic patients, especially young ones, does not preclude a normal or even better than normal vital capacity. One is tempted to speculate on the strength and elasticity of such thoracic and pulmonary structures. Second, generally speaking, the larger the residual and trapped air volumes, the worse the clinical condition of the patient. Note that the lungs of the asthmatic patient (No. 3) and the patient with emphysema (No. 4) look rather similar. However, if both patients are given a bronchodilator and the volumes are remeasured, the asthmatic patient very probably would lose some or all of his trapped air volume and some of his residual volume. The emphysematous lung will not change.

Figure 3 represents a summary of the static pulmonary volumes and the methods used. We propose the term "true total lung capacity" for the sum of the total lung capacity (as measured by spirometry and helium dilution) plus the trapped air volume (as measured by plethysmography).

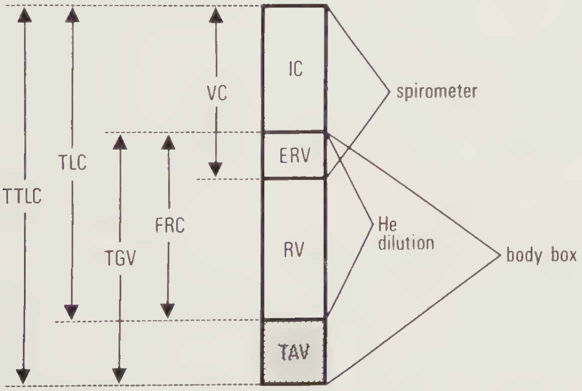

Figure 3. A review of the static pulmonary volumes and techniques used to measure them. IC, inspiratory capacity; ERV, expiratory reserve volume; RV, residual volume; TAV, trapped air volume; VC, vital capacity; FRC, functional residual capacity; TGV, thoracic gas volume; TLC, total lung capacity; TTLC, true total lung capacity. Any number of simple equations describing relationships between various volumes and capacities can be constructed from the diagram: FRC = ERV + RV or TAV = TGV – FRC. Two of them perhaps merit a more than passing interest: total lung capacity is the sum of inspiratory capacity, expiratory reserve volume and residual volume: TLC = IC + ERV + RV. For lungs containing trapped air volume, the term true total lung capacity is proposed: TTLC = IC + ERV + RV + TAV.

The reason is that this data may be useful in estimation of the degree of the hyperinflation of the lung: the trapped air volume may be quite large – 3 liters and more in exceptional cases – and play a prominent role in the enlargement of the lung. Normally inflated lung has a normal true total lung capacity, and resting respiratory position about the middle of it: in other words, residual volume plus expiratory reserve volume plus trapped air volume, if any, are about 50 per cent of total lung capacity. A hyperinflated lung has increased true total lung capacity and the resting respiratory position is shifted toward the inspirium so that the residual volume plus expiratory reserve volume plus trapped air volume, if any, are above 70 per cent of the true total lung capacity. This last requirement will rule out hyperinflation, for example, in the big lung of an oarsman: his total lung capacity is certainly increased but this is mostly due to a very large vital capacity. His resting respiratory position is usually below 50 per cent of the total lung capacity. His lung is enlarged – in the same way that his shoulder muscles are enlarged – but not hyperinflated. On the other hand, the lungs of the patients Nos. 3 and 4 in Figure 1 are hyperinflated, with increased true total lung capacity and upward shift of the resting respiratory position.

Distribution of Ventilation

The tidal volume is distributed through the airways into the functional residual capacities (sum of expiratory reserve volume and residual volume, i.e., alveolar volumes) of various sizes as shown in our patients in Figure 1. Within a pathologically changed lung, any or all of the conditions described in Figure 4 can be expected. In the asthmatic patient, alveoli of type 2 would be of course the most frequent cause of non-uniform distribution. The author's observations of changes in ventilatory distribution before, during and after an asthmatic attack may serve as an illustration. A 16 year old girl experienced a "moderately severe" attack while waiting in the laboratory after preliminary testing session. She consented to take certain tests both during the attack and after a dose of bronchodilator. These are the results of the nitrogen washout test: before the attack, the distribution of ventilation was uniform, as seen from straight washout line, but slow as seen from the slope of the line: in a normal subject, the slope would be steeper and 2 per cent nitrogen would be reached in about 10 to 12 breaths. This patient reached this limit in 24 breaths. During the attack her lung behaved as if the inspired air were distributed between at least two compartments. One was smaller, with a rate of washout corresponding to what it was before the attack: the first steeper part of the curve from breath 0 to breath 6 was indicative of this. The second compartment was larger with a slower rate of washout. Its presence and properties were revealed by the less steep portion of the curve: 2 per cent nitrogen was reached in 43 breaths.

The main cause of such non-uniform ventilatory distribution during an asthmatic attack is undoubtedly local differences in bronchial flow resistance (case 2 in Fig. 4). With at least partial relief of airway obstruction after the attack had been broken with a bronchodilator, one would expect the post-bronchodilator curve to look as something of a cross be-

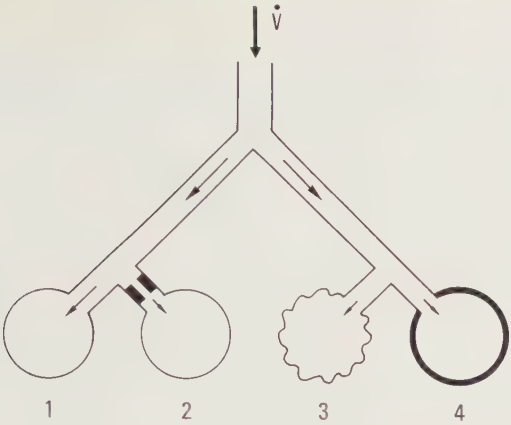

Figure 4. Usual causes of non-uniform distribution of ventilation. V̇, Ventilation in unit time; size of the arrows shows the fraction going to various groups of alveoli; 1, group of normal alveoli; 2, group of normal alveoli behind a bronchial obstruction (black sleeve); 3, group of alveoli with loss of elasticity; 4, group of alveoli with restricted expansion. The presence of a normal and of an abnormal group of alveoli, e.g., 1 and 2, divides the lung into a non-uniform system. One compartment of the system is ventilated rapidly, the other slowly.

Non-uniformity of ventilation can be determined by recording and measuring the rate and pattern of mixing of a foreign gas in the lung, for example, helium dilution in a closed circuit. The recorder traces the change in helium concentration inside the system with successive breaths. The fall in concentration is an exponential curve. If the tested lung is a one-compartment system, containing for example only alveoli of type 1, the distribution of helium would be uniform, and the behavior of the system would be described by a single exponential curve. Such a curve, plotted in semi-log co-ordinates (per cent He against number of breaths), will result in a single straight line. The slope of the line will be proportional to the rate of distribution. Its singularity will signify a uniform system. On the other hand, if the system consisted of group 1 and group 2 alveoli, the exponential curve traced by the recorder would be the result of two different superposed mixing patterns. When plotted in semi-log co-ordinates, the result would be a broken line. The part with steeper slope will show the rate of distribution of ventilation in the fast compartment, the part with flatter slope, the rate in the slow compartment. The discontinuity of the line will reveal a non-uniform system.

Many laboratories use an open circuit technique. The patient is given pure oxygen to breathe and the concentration changes of the washed out alveolar nitrogen are measured with a Lilly nitrogen-meter. Alternately, a mixture containing argon is used and the equilibration of argon with pulmonary air is monitored by a mass spectrograph. The open circuit methods are considerably more sensitive than the closed circuit method. Even so, the distribution rate of the slow compartment must be at least 50 per cent lower than the rate of the fast compartment for a difference to be detected. Both methods share a basic drawback: they can reveal a nonuniformity in ventilation; they cannot, however, determine the location of the nonuniformity in the lung.

tween the "before" and "during" pattern. If anything, it revealed a worse condition in the slow compartment: 2 per cent nitrogen level was reached after 56 breaths.

This finding is not unusual in asthmatics. The causes may be speculated upon: bronchodilator may change the local compliance patterns (case 4 in Fig. 4); or opening the previously closed bronchi and releasing trapped air may leave the lung with an additional set of unequally patent and non-uniformly conducting bronchi. This is a problem crying for a methodology more advanced than the simple washout test. Isotopic techniques obviously show future directions, in that only they can reveal the topography of distribution anomalies in the lung.

Dynamic Pulmonary Volumes and Airway Resistance

Retention and release of residual volume and trapped air volume are dependent upon the functioning of the conducting element of the lung, the bronchi. The mechanisms of the residual volume enlargement are presumably as follows. Bronchial asthma starts with an acute increase in expiratory flow resistance: with normal expiratory force the lung cannot expel the inspired volume *in the time interval available to it.* If an infinitely long time for expiration were available, the expiratory volume flow could be kept as slow as wanted; the effect of resistance then would be negligible. Because ventilation is a cyclical process and the length of cycles is determined by metabolic demands upon gas exchange, the lung cannot make the duration of expiration as long as needed. The net effect is that after each expiration a certain volume differential is kept back in the lung. The resting respiratory position is shifted towards inspirium, and residual volume increases. The chest is inflated and this in turn leads to stretching of expiratory sets of muscles (mostly internal intercostal muscles) and also of elastic elements in the lung and thorax. There is also some relief of the obstruction by increased radial pull on the airways. All these factors contribute to an increased expiratory force. Thus the equilibrium between expiratory resistance and expiratory force is re-established at increased resting volume of the lung.

In long-standing bronchial asthma, this lung inflation seems to be more or less fixated and is not released even when expiratory resistance is returned into normal range. Whether this is due to irreversible changes in thoracic and pulmonary mechanics or to reflex control of respiratory activity is not known. The problem is of importance in the rehabilitation of asthmatic patients.

It is easy to assume certain processes in the airways. However, the only way to approach the problem of obstruction is to measure the resistance to the airflow in the airways. The timed vital capacity technique described after World War II by Tiffeneau and Pinnelli in France, and by Gaensler in this country found wide use because of its simplicity, ease of calculation and good correlation with other flow measures, especially maximal breathing capacity. This technique does not measure the airway resistance directly: it only shows the maximal volume of air that can be expelled from the lungs in one second. It is assumed that with increased airway resistance this volume will be decreased. If the volume is read in liters, the result must be compared with some accepted standard, e.g., a mean value found in clinically healthy subjects of same sex, age, and body height.

Some difficulty arises in patients with considerably smaller and larger vital capacities than predicted. Consider our patient with tuberculosis, No. 5 in Figure 1. He has no airways obstruction but his forced expiratory volume in one second will be way below predicted normal value simply because he cannot even fill his lungs with the required volume! On the other hand, the youthful asthmatic patient (No. 2) might blow out in 1 second a volume close to predicted value even with some obstruction present, because of his large vital capacity.

The effect of an abnormal vital capacity can partially be compensated by calculating the result in percentage of the vital capacity. The established normal fraction, 83 per cent of the vital capacity blown out in one second, is probably too high for the general population, especially in those of advanced age. More realistic values are given in Table 1. Imagine however a 40 year old man with asthma, whose predicted forced vital capacity is 5.20 liters BTPS. His predicted forced expiratory volume in one second is 4.00 liters – 77 per cent of his forced vital capacity. His observed forced vital capacity is 4.10 liters BTPS, observed forced expiratory volume in 1 second is 2.46 liters BTPS – 60 per cent of his forced vital capacity. After using a bronchodilator his forced vital capacity increased to his predicted level of 5.20 liters BTPS, and his forced expiratory volume in 1 second increased to 3.11 liters BTPS but still remained only 60 per cent of his forced vital capacity. Thus by some indices, obstruction was substantially relieved; by another index of the same procedure it was not.

Similar considerations apply to maximal mid-expiratory flow, the other most commonly used piece of information from the forced expiratory curve. Many pulmonary physiologists hold that this index is more sensitive than forced expiratory volume in one second. When the recording of the forced expiratory volume is supplemented by simultaneous recording of flow in liters BTPS per second (usually on an x-y plotter), the resulting flow-volume curves are an even more sensitive indicator of airway obstruction. The normal curve shows a more or less linear rise, a peak flow when about 25 to 30 per cent of the vital capacity has been blown out, and an exponential drop toward zero flow (the moment vital capacity has been blown out and residual volume reached). In the asthmatic patient, the peak is reached much sooner (at 10 per cent or so of vital capacity out), is much lower, and is typically followed by a very steep drop and a low tail toward zero flow. The flow-volume curve technique, described by Hyatt and co-workers in 1961, is being currently introduced as a routine method in pulmonary function laboratories. There is no unified system of evaluation yet.

None of these techniques really *measures* the airway resistance in aerodynamic terms: the results show really how a maximal effort on part of the patient, judged in terms of ventilatory output, relates to a certain established standard. The result depends on the condition of the integrated respiratory apparatus – thoracic structures, respiratory muscles,

Table 1. *Decline in FEV_1 Expressed as Percentage of Forced Vital Capacity with Age in a Scandinavian Population*

AGE	MALES	FEMALES
20	84 ± 7.2 S.D.	87 ± 5.4 S.D.
30	80	84
40	77	82
50	73	79
60	69	76
70	66	74

Modified from Berglund, E., et al.: Acta Med. Scand., *173*:185, 1963.

resistance of the lungs, resistance of the airways, and respiratory control mechanisms. Because of the cortical effects upon the last, there is also a major psychological component: a poorly motivated patient will show a result worse than his physiologic condition would lead one to expect. In a sense, these techniques, just because they are dependent upon maximal flows, are a good measure of the overall mechanical function of the respiratory system (e.g., in exercise). They cannot give an absolute value of the airway resistance. While flow can be calculated from the expiratory curve or directly measured (in case of flow-volume curves), there are no data on alveoli-mouth pressure differences.

Even the most forceful expiratory effort comes to an end when all the vital capacity has been blown out. Why is it that the residual volume remaining in the lung cannot be exhaled? Consider the pressure changes in the chest during expiration (Fig. 5). Intrapleural pressure is reverting

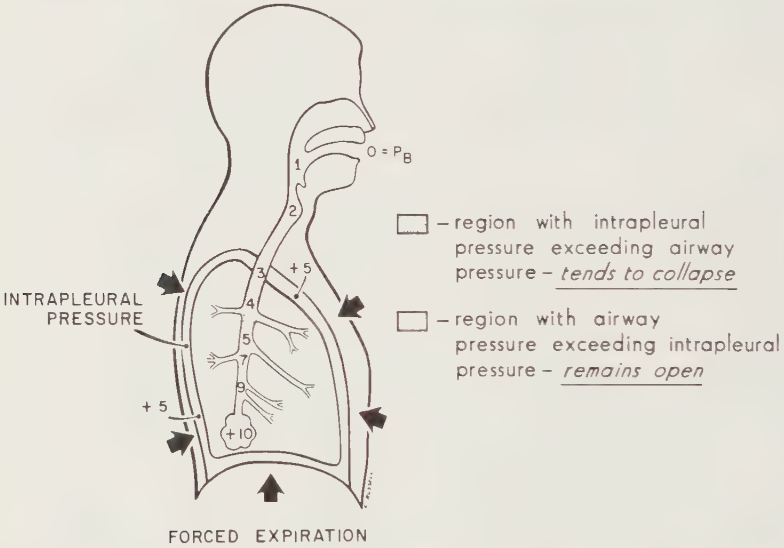
0 = P_B
1
2
3
+5
4
5
7
9
+10
INTRAPLEURAL PRESSURE
+5
FORCED EXPIRATION
▨ – region with intrapleural pressure exceeding airway pressure – tends to collapse
☐ – region with airway pressure exceeding intrapleural pressure – remains open

Figure 5. Pressure relationships in the thorax on forced expiration. Dark arrows, expiratory forces; +10 (in the alveoli) to 0 (at the mouth), gradients in intra-alveolar and intra-airways pressure; P_B, barometric pressure. All pressures are expressed in mm. Hg. Intrapleural pressure is normally slightly negative, −5 mm. Hg in this figure. Alveolar pressure under conditions of no flow, e.g., at the end of inspiration, is equal to barometric pressure. On forced expiration, the action of expiratory forces produces a pressure increase of 10 mm. Hg throughout the thoracic structures. Alveolar pressure rises by this amount. The pressure gradient between alveoli and the mouth is the force that gets the gas content of the lung into outward motion. The force is naturally dissipated by its action (by airway resistance mostly) as seen from the gradient diminishing along the airways and disappearing at the mouth (pressure here equal to P_B, gradient zero). The negative intrapleural pressure is reversed into positive but does not reach the alveolar pressure:

$$P_{IP\,EX} = P_{IP\,R} + 10 \text{ mm. Hg}$$

$$P_{IP\,EX} = -5 \text{ mm. Hg} + 10 \text{ mm. Hg} = +5 \text{ mm. Hg}$$

where $P_{IP\,EX}$ is the intrapleural pressure during forced expiration; $P_{IP\,R}$ is intrapleural pressure at rest. As the driving pressure is dissipated along the airways during forced expiration a region is reached where the airways pressure is equal to the intrapleural pressure; downstream from here the intrapleural pressure is higher than airways pressure, and if the mechanical conditions of the airways allow it, the airways will collapse. The airways collapse is the limiting factor of forced expiration. (*From* Slonim, N. B., and Hamilton, L. H.: Respiratory Physiology. St. Louis, Missouri, C. V. Mosby Co., 2nd ed., 1971, by permission.)

to positive values with increasing expiratory efforts. At a certain level of the bronchial tree the pressure transmitted through the lung parenchyma to the airways becomes higher than the forces that keep the airway open: namely, the transbronchial pressure and the mechanical rigidity of the bronchial structure (the shaded region in Fig. 5). The airway then collapses *and any further expiratory effort closes it even more.* The volume of air still present in the alveoli when the closure occurs is of course the residual volume. Not all bronchi, however, collapse at the same time during deep expiration. The resting intrapleural pressure is not the same throughout the chest in the upright position: because of the weight of the lung, the basal portion of the lung tends to develop a pressure on the enveloping thoracic structures; the apical portion develops a pull. Therefore the intrapleural pressure in the basal region is close to zero or may even be positive, while in the apical region it is decidedly negative. Thus during deep expiration, the closing pressure develops much sooner in the basal than in the apical region.

This feature of the lung is the basis of the measurement of the closing volume, defined as that percentage of vital capacity remaining in the lung when a recognizable break in the nitrogen concentration tracing occurs – in other words, when some of the bronchi begin to close. Thus if a patient's closing volume is measured as 35 per cent of vital capacity, it means that some of his bronchi begin to close when he has expired 65 per cent of his vital capacity and has 35 per cent to go. Closing volume in normal subjects is age-dependent (see Table 2). Closing volume (in a given age group) seems to be higher in females. The difference is small but statistically significant. It may be expected that closing volume will be higher in lungs with loss of elasticity (e.g., in emphysema) or in lungs with already narrowed bronchi (e.g, in asthma). The technique is especially useful in cases of a beginning airways disease still below the threshold of other functional tests.

The effect of intrapleural pressure reversal upon bronchi during forced expiration is modified remarkably by the presence of an obstruction. Imagine that there is in Figure 5 an expiratory obstruction in the region of number 9 (see also Table 3). Anatomically, this is in the so-called small airways (diameter less than 1 to 2 millimeters). The pattern of the dissipation of expiratory force becomes uneven: most of the force will be used to overcome the obstruction. This will result in a different pressure gradient along the airway: from the alveoli down to the obstruction there will be little loss of pressure, through the obstruction there will

Table 2. *Mean Values for Closing Volume in Different Age Groups*

AGE	NO. OF SUBJECTS	CLOSING VOLUME AS PER CENT OF VITAL CAPACITY
7–16	12	8.7
20–29	18	9.0
30–39	15	14.6
40–50	9	20.9

From Anthonisen, N. R., et al.: Resp. Physiol., 8:58, 1969, with permission.

Table 3. *Pressure Gradients (in mm. Hg) from Alveoli to Mouth Indicating Zone of Collapse (frame) on Forced Expiration*

	NORMAL	SMALL AIRWAYS OBSTRUCTION	LARGE AIRWAYS OBSTRUCTION
Alveoli	10	10	10
	9	9.5	9.7
	8	Obstruction	9.4
	7	5.5	9.1
	6	$\boxed{4.5}$	8.8
	5	$\boxed{4}$	8.5
	$\boxed{4}$	$\boxed{3.5}$	Obstruction
	$\boxed{3}$	$\boxed{3}$	$\boxed{4.5}$
	2	2	$\boxed{3}$
	1	1	1
Mouth	0	0	0

be an abrupt and rather significant loss, and downstream from the obstruction there will be a gradual loss as before (although at a different absolute level). Obviously, the airways *upstream* from the obstruction will be protected against collapse, airways *downstream* from the obstruction will collapse much more readily with the same intrapleural pressure change. All the maximal flow dependent measures – forced vital capacity, forced expiratory volume in one second, maximal mid-expiratory flow, etc. – will be less than normal, because of this premature collapse of the airways. Imagine now a similar obstruction further downstream, e.g. at number 4. This would be in the so-called large airways (diameter more than 2 millimeters). Again, the airways upstream from the obstruction will show little loss of pressure, there will be abrupt and considerable loss of pressure in the obstruction, and a gradual loss toward the mouth from the obstruction down. In this case, however, because of the shorter distance to the mouth, the size of the collapsing zone is comparable to normal conditions. Table 4 shows hypothetical pressure gradients in a normal lung, and the effects upon them of the two types of obstruction. The effects of an *added* large airways obstruction (unless it is very large) can be for the most part overcome by increased expiratory effort, especially in the initial phase of expiration. The conclusion is that the maximal flow dependent measures are much more affected by small airways obstruction than by large airways obstruction.

If the maximal flow techniques take care of small airways, what about the determination of the large airways obstruction? The technique of body plethysmography is used for this purpose. Volume flow during the panting in the box is very low; we know that volume flow in a given airway is the product of driving pressure and the fourth power of the airway radius. For a given volume flow in airways with a very large total square section, the driving pressure becomes then very small, in fact *beyond* the sensitivity of the routinely used instruments. The resistance is measured by the box in terms of pressure difference in centimeters of water required to move 1 liter of air per second; obviously a zone must be reached in the bronchial system (going from trachea upstream) where the required pressure difference would become nonmeasurable. This is probably around the tenth generation of branching – the boundary between large and small airways. This is not to say that small airways do not contribute to total airways resistance: they do, *but under usual conditions this contribution cannot be recognized by body plethysmography.* In pathologic conditions, the obstruction in the small airways would have to be very marked before it would influence the body box measurement. Naturally, as with the maximal flow dependent measures, no absolute statement can be made. Thus when the body box shows an increased value of resistance, there is a high probability that the obstruction is located in the large airways.

Body plethysmography, then, measures resistance in the physical terms of pressure and flow. The reciprocal value of resistance is often used – airway conductance, defined as the number of liters of air that can be moved from alveoli to the atmosphere in 1 second when the pressure difference is 1 centimeter of water. The airway conductance varies directly with the volume of the lungs during the measurement. Because the lung volume in asthmatic patients may change, e.g., after administration of bronchodilators, the airway conductance is usually corrected for it and is then called specific airway conductance:

$$SG_{AW} = \frac{G_{AW}}{V_L}$$

where SG_{AW} is the specific airway conductance; G_{AW} is the airway conductance ($= 1/R_{AW}$); V_L is the volume of the lung during the measurement, usually functional residual capacity or thoracic gas volume. Anatomic features of the airway also influence the resistance, which varies markedly with age in children (Table 4).

The relationships between airway resistance and lung volume sometimes change in asthmatic patients in a very interesting way: Table 5

Table 4. *Airway Resistance and Airway Conductance in a Group of Normal Children of Both Sexes and Various Ages*

AGE	R_{AW}	G_{AW}
7	7.4	0.135
8	6.5	0.154
9	5.7	0.186
10	5.0	0.200
11	4.2	0.238
12	3.7	0.270
13	3.1	0.323
14	2.6	0.384
Adults	0.5–2.5	2.00–0.400

Data of Poppell et al. from the Pulmonary Functions Laboratory, National Jewish Hospital and Research Center, Denver, Colorado.

Table 5. *Pulmonary Values in a 26 Year Old Woman (Weight 167 lb., Height 63")*

MEASURE	PREDICTED	OBSERVED	
		Before Bronchodilator	After Bronchodilator
FRC (Liters BTPS)	2.50	3.15	3.90
TGV (Liters BTPS)	2.50	4.03	4.00
TAV (Liters BTPS)	None	0.88	0.10
R_{AW} (cmH_2O/L/sec)	0.50–2.50	3.50	4.50
G_{AW} (L/sec/cmH_2O)	2.00–0.40	0.286	0.222
SG_{AW} (L/sec/cmH_2O/LTGV)	0.80–0.16	0.071	0.053

FRC: functional residual capacity, by helium dilution
TGV: thoracic gas volume, by body plethysmograph
TAV: trapped air volume, as TGV − FRC
R_{AW}: airway resistance
G_{AW}: airway conductance
SG_{AW}: specific airway conductance

From the Pulmonary Functions Laboratory, National Jewish Hospital and Research Center, Denver, Colarado.

shows that this patient had a definite trapped air volume and a moderate obstruction; after a dose of bronchodilator, the trapped air volume was completely released but the airway resistance rose to between moderate and severe obstruction. Our interpretation: the bronchodilator opened the until now closed (to helium) bronchi (Fig. 2) so that functional residual capacity increased and trapped air volume was released. The bronchi, however, were opened only to less than normal diameters. In fact, an additional set of resistance elements had been added to the airways, and the overall resistance rose. Such a case should be recognized as different from a paradoxical reaction to bronchodilators.

Small airways, by virtue of their enormous total square section, constitute in Macklem's words a silent zone in which there may be considerable airway obstruction resulting in little or no abnormality in the usual tests of pulmonary function. A more sensitive and more specific method is needed for small airways resistance than the maximal flow-dependent measures. It seems that a promising one has been found in the determination of the so-called frequency-dependent compliance. In measurement of lung compliance, the lung should be in static condition, e.g., at the end of inspiration or expiration, and some time must be allowed for pressures and volumes to equalize. This is sometimes very difficult for asthmatic patients: they simply cannot hold their breath, even for a short time, especially at small lung volumes. This eventually led to the discovery that there is a relationship between respiratory frequency and the value of compliance, if there is an increased resistance. There is no marked dependence in healthy subjects up to respiratory frequency of 60 to 90 breaths per minute. There is, however, a pronounced dependence in patients with obstruction. In case of acute bronchitis, dynamic compliance at frequencies up to 10 breaths per minute was equal to static compliance (and both agreed with pre-bronchitis values in the same subject). With increased respiratory frequencies, the dynamic compliance dropped to 75 per cent at 45 breaths per minute, to 65 per cent at 100 breaths per minute, and to 50 per cent of the static compliance at 130 breaths per minute. Results such as this are to be expected if the obstructions are in small airways, are non-uniform, and are randomly distributed through the lung. Informative and very sensitive as this method is, it provides only an empirical index of increased resistance of the small airways, and not an absolute measurement.

Diffusing Capacity of the Lung

The diffusing capacity of the lung as measured by the carbon monoxide method depends primarily on four factors; (1) the area of the lung membrane through which the gas diffuses ("lung membrane" means the whole system of diffusion barriers in the lung); (2) the properties of the lung membrane; (3) the rate of reaction of carbon monoxide with hemoglobin; and (4) the volume of pulmonary capillary blood.

In asthmatic patients the diffusing capacity is often elevated. It has been shown that the elevation is a function of total lung capacity (at least in young asthmatics); in other words, it is proportional to the area of the lung membrane. This area is of course increased in the almost always enlarged lungs of asthmatic patients. When isoproterenol is given to such patients, more often than not there is a drop in diffusing capacity—sometimes a very marked drop. There is usually no change in total lung capacity, therefore no change in the area of the membrane.

The finding was rather puzzling until Gazioglu and co-workers[8] analyzed it in more detail. Diffusing capacity can be calculated in terms of its components:

$$\frac{1}{DL_{CO}} = \frac{1}{D_M} + \frac{1}{\theta \times V_C}$$

where DL_{CO} is the diffusing capacity of the lung for carbon monoxide; D_M is the diffusing capacity of the membrane; θ is the reaction rate of carbon monoxide with hemoglobin; and V_C is the pulmonary capillary blood volume.

The reaction rate is proportional to the amount of available hemoglobin, to the oxygen tension, and to the permeability of red blood cells to carbon monoxide: it can be calculated from given data. Diffusing capacity of the membrane and capillary blood volume can be calculated from values of DL_{CO} and θ determined at two considerably different tensions of oxygen. This method was used in patients with the drop in diffusing capacity after isoproterenol. It was found that isoproterenol has no effect upon the membrane or upon reaction rate; it decreases, however, the capillary blood volume, and therefore the DL_{CO}.

Ventilation/Perfusion Relationships

A definite though not very marked arterial hypoxemia was observed after isoproterenol in the same series of asthmatic patients described above. The impairment in diffusion was not enough to explain this. A more detailed analysis revealed that a mismatching of ventilation and perfusion (Fig. 6) was present, with increased numbers of alveoli of type 2 or even type 4. An increased number of alveoli of type 2 or 4 may be due either to increasingly non-uniform ventilation, shunting more air away from perfused alveoli (not probable after bronchodilator), to emphasized non-uniformity in distribution of ventilation and perfusion simultaneously, or more simply to increased perfusion of already nonventilated alveoli (most probable after isoproterenol, owing to its cardiovascular effects). Thus the mismatching of ventilation and perfusion is the main cause of the decreased arterial oxygen tension so often observed in asthmatic patients even before any drug is administered.

Ventilation/perfusion mismatching is even more complicated (and more important) in status asthmaticus with its inherent ventilatory pathology. The oxygen content of alveolar air in these patients varies from almost normal to low when large non-uniform obstructions are present. Carbon dioxide content varies from normal to hypercapnic to hypocapnic. Thus in a large group of children in status asthmaticus, 45 per cent had normal Pco$_2$, 47 per cent had elevated Pco$_2$ (some of them more than 60 mm. Hg with a pH below 7.3), and 8 per cent had a decreased Pco$_2$. In the patients with elevated Pco$_2$ there obviously was present a respiratory acidosis with retention of CO$_2$ because of obstruction. In a few cases it was combined with metabolic acidosis, presumably because of increased respiratory work, hypoxia, and perhaps inadequate caloric input and dehydration. Patients with decreased Pco$_2$ hyperventilated. The ratio of hyperventilating patients to others varies considerably, perhaps because of psychological reasons. Alveolar air, or rather alveolar carbon dioxide, is the volatile part of the carbonic acid-bicarbonate buffer system. Thus its disturbances play the same role as in other disease with altered acid-base balance, and for the same reasons. While very often present in asthma, such disturbances are secondary to the causative features of the disease.

EVALUATION OF PULMONARY FUNCTION TESTS

It would be impractical and expensive for a patient to undergo all the tests mentioned, even if they were routinely available, which they are not. Those tests routinely available (and if not, should be) include spirometry, a functional residual capacity measurement, a diffusing capacity test, and arterial blood gas determinations. From these studies, it is possible to obtain the necessary information for the diagnosis and treatment of the asthmatic patient.

Vital capacity, expiratory reserve volume, functional residual capacity and residual volume distinguish between restriction and increased volume. A forced vital capacity, as compared with a leisurely vital capacity, allows evaluation of significant airway collapse secondary to rapid changes in intrapleural pressure. The FEV$_1$ expressed as a percentage of the forced vital capacity (FEV$_1$/FVC) is a good indicator of large airway resistance, while the SG$_{aw}$ approximates resistance in the small airways.

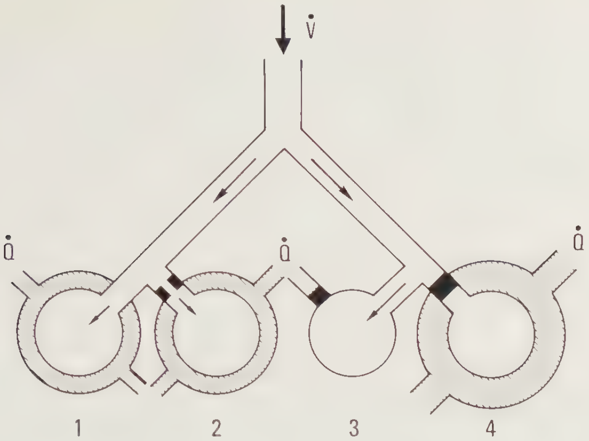

Figure 6. Relationships between ventilation and perfusion of the lung. $\dot{V}$, Total ventilation; arrows, distribution of various amounts of ventilation to various alveoli; $\dot{Q}$, perfusion with blood of various alveoli; 1, normally ventilated and perfused alveolus; 2, hypoventilated and normally perfused alveolus; 3, hyperventilated and nonperfused alveolus; 4, nonventilated and hyperperfused alveolus.

In a normal subject at rest, the alveolar ventilation may be 4.5 liters per min. and the blood perfusion may be 5.0 liters per min.; the ratio of alveolar ventilation to perfusion is 4.5 over 5.0 = 0.9. Such a condition, illustrated in alveolus No. 1, is ideal for normal gas exchange, and is present in at least 70 per cent of alveoli in normal young subjects. A normal lung as a whole has this average ventilation-perfusion ratio. In some alveoli however, the matching of ventilation to perfusion is not ideal. In alveoli similar to No. 2 there is normal blood perfusion but ventilation is for some reason diminished, e.g., by obstruction. Such alveoli are underventilated relative to their perfusion. Blood flowing through them is insufficiently saturated with oxygen. Such alveoli contribute to the venous admixture to arterial blood. In alveoli of type 3 there is no perfusion at all. They are, however, more than normally ventilated. Because there cannot be any gas exchange between alveolar air and blood (there is no blood available), such alveoli are part of the respiratory dead space. Finally, No. 4 represents alveoli without ventilation but with more than normal perfusion. Because there cannot be any gas exchange between alveolar air and blood (there is no air available), these alveoli are part of the venoarterial shunt. Thus any degree of lessened perfusion (down to complete absence) causes a rise in respiratory work because of increased dead space ventilation; any degree of lessened ventilation (down to complete absence) causes hypoxemia. A fatal hypothetical case would be a lung consisting only of alveoli No. 3 and No. 4: such lung may have a normal total ventilation and normal total perfusion. However, it would be worthless, because all ventilation is distributed to the dead space of nonperfused alveoli, and all perfusion is distributed to the shunt around nonventilated alveoli. Naturally, every functioning lung consists of alveoli of all types, those within normal range of ventilation and perfusion prevailing. The ratio of ventilation to perfusion for the whole lung can be calculated from this equation:

$$\frac{\dot{V}_A}{\dot{Q}} = \frac{1}{K} \times \frac{C_{\dot{v}CO_2} - C_{aCO_2}}{P_{ACO_2}}$$

where $\frac{\dot{V}_A}{\dot{Q}}$ = ventilation-perfusion ratio; K = a conversion constant including gas reduction factors, under normal conditions equal to 8.63; $C_{\dot{v}CO_2}$ = concentration of CO_2 in mixed venous blood in volume per cent; C_{aCO_2} = concentration of CO_2 in arterial blood in volume per cent, P_{ACO_2} = tension of CO_2 in the alveoli in mm. Hg. The collection of these data requires right heart catheterization for mixed venous blood, and arterial puncture for concentration and carbon dioxide tension. A number of noninvasive methods have been designed. Some of them, using the radio isotopic techniques, are the only ones that can show the topography of ventilation-perfusion mismatching in the lung.

Changes before and after use of a bronchodilator indicate the reversibility of the obstruction and by comparing the FEV_1/FVC and the SG_{AW} the area(s) of reversibility are approximated. If determination of the true total lung capacity is needed, planimetry of a chest roentgenograph correlates well with the thoracic gas volume obtained with the "body box" and is easily done. A diffusing capacity will eliminate emphysema as a diagnostic consideration, since in emphysema it will be low, while in asthma it will be normal to high. Arterial blood gases will give a good approximation of ventilation/perfusion abnormalities, as oxygen is very sensitive to these parameters. These studies, while not inexpensive (average cost should be in the area of $100 to $175) allow accurate diagnosis and form a good baseline with which to follow the course of the patient. A vital capacity and FEV_1, which are often substituted for the full spirometric studies, add nothing to a careful and competent examination of the chest of the patient. Measurement of diffusing capacity, lung volumes, and arterial blood gases give data which is not available by physical examination. Follow-up examination of the patients can be done by spirometry (complete), with the assumption that volume changes (residual, functional, and total) will not decrease as the reversibility of the flows diminishes or becomes worse, but that they will also become worse. The statistical relationship between flow changes and volumes is unknown. The extent and time of re-evaluation should be dependent on the course of the disease.

The answer then to the original question, "Pulmonary functions in asthma – are they worth it?" is an unqualified yes. They will not substitute, however, for a careful history and examination; therefore those tests ordered must be complete enough to add information to the examination and to exclude other conditions which tend to mimic asthma. Along with history, they are indicators of the progress of the disease and are useful in the evaluation of therapy.

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Specific Therapy In Allergy

Pro (With Reservations)

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That the distinguished Editor of this issue on Allergy of the *Medical Clinics of North America* has asked two authors to write on the subject of "specific" treatment is indicative of the differences of opinion which exist in respect to the value of, and indications for, this mode of therapy. "Specific" treatment by giving injections of the very allergenic substances which cause symptoms of disease when introduced by other routes was inaugurated in 1911[1] and has become ingrained in the practice of specialists in allergy. Both allergists and non-allergists have from time to time asked serious questions both about the rational basis for such treatment and its efficacy in clinical practice. Particularly, those non-allergists who have not observed results in long series of patients treated over months and years have been critical of subjective evaluations made by those whose livelihood may depend on continued use of such techniques.[2] So long as only subjective evaluations were available, discussions of specific immunization tended to become polemics exposing mainly the prejudices of the participants. Objective evaluations, however, now allow one to examine some hard won facts arising out of scientific investigation and thus to find a more rational basis for arriving at an opinion.

The extent to which not all pertinent facts are known still leaves many points moot and therefore highly arguable. My preference is not to argue such matters but simply to point out that they still lack final determinations. On the other hand, the considerable body of scientific evidence that exists does allow the development of a rational philosophy for the employment of specific therapy. The discussion which follows, therefore, will be confined to that information obtained from planned collection of data relevant to specific therapy and the conclusions that can be

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drawn from such data. Studies of series of patients treated in the course of regular practice without controls have intentionally been omitted.

The development of additional data may, in the future, both require changes in current conclusions and allow conclusions about matters now obscure, so that the viewpoint presented is a dynamic one and subject to change. It is, however, a basis for the practical use of injection treatment by allergists and for the intelligent referral of patients to allergists for such treatment on the part of family physicians, internists, and pediatricians.

Noon's first trial of prophylactic inoculation in 1911 was entirely concerned with grass hay fever.[1] His theory of hay fever was that it arose from toxic substances present in pollens. Stimulated by reports of antitoxic immunity in diphtheria, he hoped that "antitoxins" elicited by a series of inoculations would protect against the supposed pollen toxins. His first trial in a series of hay fever patients showed that inoculations of boiled grass pollen extract caused a reduction in the patients' reactivity to fresh pollen instilled in the eye. This appeared to be accompanied by less severe symptoms during natural seasonal exposure to the pollen. Freeman[3] extended this work and observed clinical protection in a larger group of patients and noted that asthma during the pollen season was also relieved.

It soon became evident, however, that pollen allergy did not arise from toxins in pollens but from a phenomenon similar to anaphylaxis in animals because of the development of specific sensitizing antibodies in the affected individual. The efficacy of inoculation was then attributed to a phenomenon akin to "desensitization" first observed in anaphylactically sensitive animals.[4] Sublethal doses of antigen appeared to exhaust temporarily the antibodies responsible for the sensitivity and to allow further exposure to formerly lethal doses without harm. The term desensitization became extensively employed to describe the inoculation process and the use of the method was extended from pollens to molds, dusts, animal danders, and many others, often without the careful observation that had characterized Noon and Freeman's work. As it was apparent that most patients were incompletely "desensitized" and could still react if given a large enough exposure, the term "hyposensitization" came into use as being more exactly descriptive of this state of affairs. There was little insight into the mode of action of such treatment except that obtained from animal experimentation with anaphylaxis until Cooke et al.[5] reported the discovery of "blocking" antibodies by showing that patients undergoing desensitization developed circulating antibodies which specifically blockaded the Prausnitz-Küstner reaction to the allergens being used in treatment.

For years there was little attempt at systematic collection of data concerning the issue central to clinical acceptance of a method of treatment; namely, does it relieve the disease under treatment? In addressing this question, three principal requirements must be met in putting it to a rigorous test: (1) In a highly variable disease, treated patients must be compared with similar patients who go without treatment. (2) A method of evaluation of progress of the condition must be employed which can be subjected to a statistical analysis to test the hypothesis that the results observed could have occurred by chance alone. (3) Techniques are necessary to eliminate or at least make allowances for the bias of the investigator and the subjects.

With respect to the first requirement, it should be clear that patients with allergy to different agents and with differing manifestations, i.e., asthma, hay fever, urticaria, cannot be lumped together in a single study of treatment. Although hay fever and asthma, for instance, are both allergic conditions and may be caused by the same inhaled allergens, they probably differ considerably in their pathogenesis and may respond quite differently to treatment. By the same token, grass pollen allergy may respond quite differently to treatment than, shall we say, house dust allergy. Selection of patients for a satisfactory treatment study requires therefore a reasonably homogenous condition (such as hay fever) caused by a definable allergen (plant pollens are particularly good). As the severity of disease depends on degree of exposure, some homogeneity of exposure is also required.

With respect to the second requirement, objective measurements of allergic disease have not been possible. Although precise measurements of the state of either the nasal airway or the bronchial airway are possible, such measurements, taken at a moment in time, do not reflect the state of disease over a period of days, weeks or months. To date, we are dependent largely on the patient's perception of disease. Data collection, therefore, depends on frequent assessment of the patient's perceptions, and is best done by symptom diaries, where the patient daily or, better still, several times daily, enters specific ratings as to the severity and duration of specific symptoms of disease. Such information can be reduced to numbers manageable by a number of standard statistical methods.

Elimination of bias is best achieved by use of the double-blind techniques developed by clinical pharmacologists. Untreated control patients receive inert placebos not distinguishable by appearance from the "real" medicine given the patients under treatment. The investigator also does not know which patients receive placebo and which receive active medication. Such precautions are particularly important when objective measurements are not available and subjective evaluations from patient and physician are the only means of assessing results.

A number of studies which meet these three requirements more or less rigorously are available for review and do provide a body of evidence for use in evaluating clinical efficacy. As might be expected, results are somewhat different with various allergens and with various manifestations of allergy, so it is worthwhile to review these findings in some detail, exposing some of the distinctions developed.

The first controlled study was reported in 1954 by Frankland and Augustin[6] in the disease studied by Noon and Freeman, grass pollen hay fever and asthma. Two hundred patients were under study, 100 receiving treatment with one or the other of two allergenically potent grass pollen extracts and 100 receiving placebos. Assessments by blinded physician review with the patients of a single season of exposure showed that 78 of the hay fever patients had good or excellent results following pollen treatment, whereas only 33 of the patients receiving placebo had similar results. Of 31 of the pollen-treated patients who also had seasonal asthma, 29 had good or excellent results with the asthmatic symptom. Of 26 of the placebo patients with asthma only 8 had good or excellent results. In both hay fever and asthma, the differences were highly significant ($p = .001$). McAllen et al.[7] further studied grass pollen desensitization in grass pollen asthma, employing a depot of grass pollen allergen. Although the numbers were small, 18 of 24 patients treated for 1 year and 12 of 15 patients treated for 2 years showed evidence of "protection" on bronchial challenge. Clinical results did not always correlate with "protection" from bronchial challenge. The lack of untreated control patients in this study makes it impossible to assess the significance of the results.

Disease caused by ragweed pollen has been studied much more thoroughly because of the prevalence of this condition in the United States and Canada. Johnstone[8] studied both hay fever and seasonal asthma due to ragweed pollen in 112 children. One group of 29 patients received the highest tolerated dose of ragweed pollen extract while the remainder consisted of 3 groups receiving either tiny doses of pollen extract or placebos. The rate of improvement of hay fever symptoms according to mothers' responses to questionnaires was greatest in the high dosage group. The low dose groups and the placebo groups had much lower rates of improvement. In the high dosage group 68 per cent lost their asthma whereas only 19 and 7 per cent of the low dosage and placebo groups lost their asthma. The difference in results between control and "high" dose group was highly significant by chi square test ($p < .001$).

Lowell and Franklin[9] compared the effects of ragweed pollen extract with a placebo of histamine in 24 ragweed hay fever patients over two seasons. Symptom scores from daily diary cards were significantly lower in the specifically treated group during the weeks of maximum ragweed pollination.

Lowell and Franklin[10] later collected 24 patients from their clinic receiving desensitization for ragweed and other allergens. In a double-blind fashion half of these patients had the ragweed extract withdrawn from their treatment mixture about 5 months before the expected appearance of ragweed pollen; the other half were continued on therapy. When the patients kept a detailed diary of symptoms, there was a significant difference ($p < .01$) in the hay fever symptoms of the two groups during the week of heaviest pollen exposure, with the treated group faring better than the group whose ragweed treatment had been withdrawn. This study was interpreted to indicate that desensitization is indeed specific for the allergens administered and tends to be lost wholly or in part at least 5 months after discontinuance.

Although favorable results were noted in the foregoing studies, Fontana et al.[11] were unable to demonstrate convincing or significant therapeutic results over a period of 5 years in a controlled double-blind study conducted in children with ragweed hay fever. The parents of the patients under study filled out a symptom diary which was returned at weekly intervals. The diary was scored for the presence or absence of symptoms on each day, but not for the severity or duration of symptoms.

There was no difference in the number of days with symptoms referable to hay fever in the specifically treated and the placebo treated patients. The measuring stick for evaluation of results in this study was quite different from that of earlier studies and might not detect the degree of amelioration observed earlier.

In 1963 our laboratory and clinic at Johns Hopkins initiated a series of studies with ragweed hay fever, designed to resolve some of the issues raised about clinical efficacy and at the same time to explore the presumably immunologic mechanisms leading to modification of the patients' symptoms. These immunologic observations will be described later in this review but at this point it is appropriate to outline briefly the clinical results. The principal allergen of ragweed pollen (antigen E) had recently been isolated and it had been shown that this simple protein, although only 6 per cent of the extractable protein of the pollen, accounted for 90 per cent or more of the allergenic activity of pollen extracts. Treatment was therefore undertaken with purified antigen E as well as the crude whole extract. Results were quite similar with the crude and purified material, so for the most part the two substances will not be dealt with separately.

Patients living in the Baltimore area were selected on the basis of a history of hay fever symptoms during the ragweed hay fever season and positive skin tests to small amounts of ragweed extract and the demonstration of histamine release from isolated washed leukocytes in vitro upon exposure to ragweed extract. (It has since been demonstrated that this is a reaction mediated by specific ragweed IgE antibodies fixed to basophils.) Initially patients were assigned at random to either a treatment group or a placebo group. In later years, after it was found that the results of quantitative histamine release tests could predict the severity of symptoms during natural exposure rather accurately, patients were matched with partners of similar sensitivity and members within the group assigned to treatment groups or placebo groups randomly. Assessment of results was by symptom diaries, filled out twice daily during the ragweed season, and collected weekly for analysis.

In the first 2 years, when rather low doses of ragweed antigen were employed, there was little difference between the symptom scores of specifically treated patients and placebo treated patients. The same patients (with some additions to replace dropouts) were continued in subsequent years with an increase of dose each year and at first significant ($p < .02$) and then highly significant differences ($p < .001$) in symptomatology began to emerge.[12] Figure 1, from 1968, shows the daily difference in averages of symptom scores in three groups of about 20 patients each treated with placebo, antigen E, or whole ragweed extract in that year. Figure 2 is a scattergram of individual patient seasonal scores over 6 years and shows the decreasing severity of symptoms reported as the dose received escalated each year. Both these figures illustrate the important point that the treated patients did not, by and large, experience a complete cure of their disease, only a measurable and significant degree of amelioration of their symptoms.

Another fact was noted in this initial series of studies, i.e., once a sat-

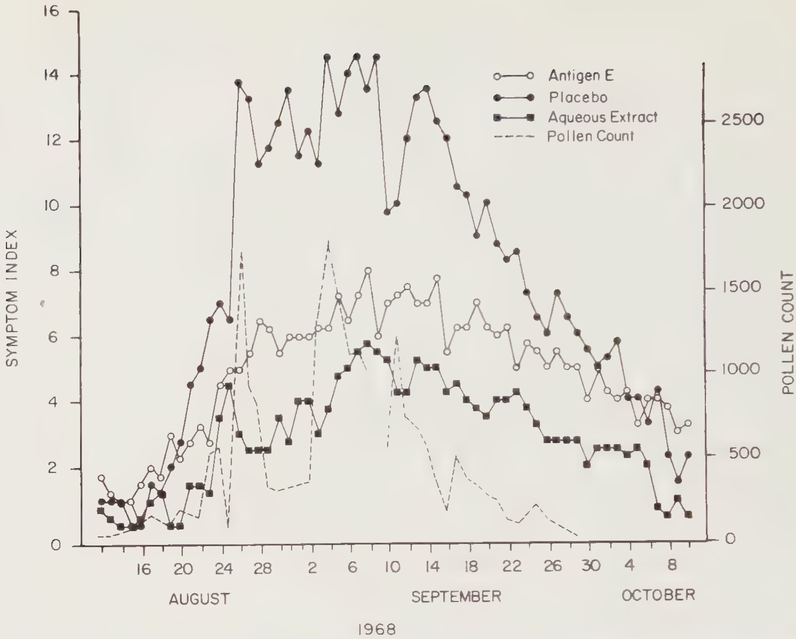
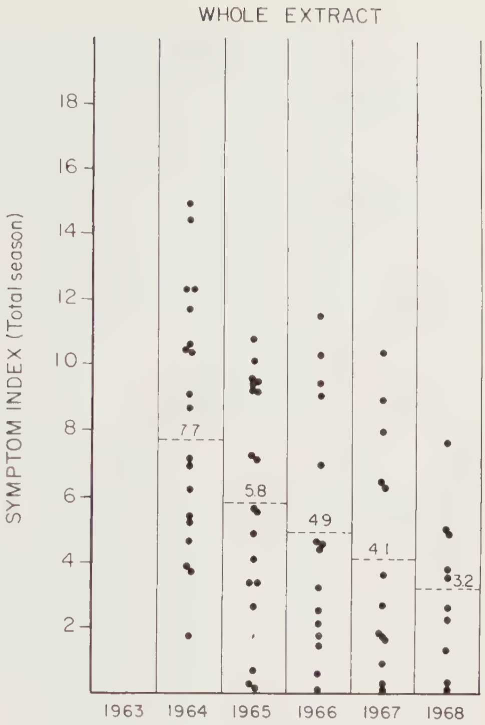


Figure 1. Average daily symptoms scores for groups of ragweed hay fever patients undergoing maintenance immunotherapy in 1968.

isfactory dosage level was reached relatively infrequent booster injections would maintain the clinical efficacy of treatment. For 2 years running, clinical improvement was maintained by 8 booster injections a year at 6 week intervals.[13]

As this study had employed gradually increasing doses over several years, it was not clear whether results were a strictly dose related phenomenon or represented a cumulative effect of all past dosage. For that reason, in 1968, a new study was organized with patients not heretofore given injection treatment, administering the larger dose in a single year. The results were entirely similar to those observed in the earlier groups after several years and seemed to strengthen the notion that symptom relief is a dose related phenomenon.[14] It has not been possible, however, because of allergic reactions to injected extract, to explore the effects of ever increasing doses to determine whether complete cures are possible. Such reactions are of two types: local reactions in the form of 1 or 2 day painful, itchy swellings at the site of injection and systemic reactions starting shortly after injection in the form of hives, angioedema, asthmatic symptoms and, in the extreme case, anaphylaxis. Further exploration in dosage has taken the form of attempting to slow absorption to prevent rapid allergic reactions after injection. Alum-precipitated ragweed extract showed evidence of slower absorption in the form of a reduced incidence of systemic reactions, and clinical and immunologic results were



	1963	1964	1965	1966	1967	1968
No Injections		16	16	16	8	8
Average dose (PNU)		829	2,442	9,483	9,636	24,132
No Patients		19	19	15	13	10

Figure 2. Average *individual* daily symptoms scores during the hay fever season in patients receiving whole ragweed extract immunotherapy over several years.

as good as with regular soluble extract. A great increase in dosage could not, however, be achieved.[15]

Emulsification of extracts in mineral oil has also been tried. In our hands these emulsions were not highly effective.[16] The demonstration that a large dose of mineral oil induces myeloma formation in mice probably effectively prevents its widespread acceptance in man.

Detoxification of pollen extracts may also allow the safe employment of much larger doses. Treatment of pollen extracts with formaldehyde causes the formation of "allergoids," substances with a reduced capacity to elicit allergic reactions but a retained capacity to cause antibody formation.[17] Such substances are currently under trial.[18]

Desensitization to allergens other than common plant pollens has been studied less completely. House dust is a common allergen and has been considered particularly in perennial asthma. As house dust extract is prepared either from vacuum cleaner sweepings or mattress dust, it represents a heterogenous mixture of mold, insect parts, bacteria, vegetable fibers, human and animal danders, and much else. Since house dust extract is essentially uncharacterizable, it is impossible to compare different extracts for content of known materials. Nevertheless, positive dermal reactions to dust extracts are common in patients with allergic symptoms and the presence of one or more specific allergens peculiar to house dust has often been postulated. The frequent presence of dermal reactions in atopic individuals has led to attempts at desensitization with house dust extracts. In recent years several attempts have been made to evaluate results in blinded, controlled studies.

The British Tuberculosis Association[19] reported a cooperative study in which 33 asthmatic patients received injections over 18 months while 37 patients received placebos. Symptom scores, time lost from work, medication usage, and expiratory flow rates were not significantly different in the two groups.

On the other hand, Aas[20] has presented a more complete evaluation of house dust treatment in 80 children. Two commercial house dust extracts, "A" and "B," were compared with placebos in a program of $2\frac{1}{2}$ to 3 years of injections. Bronchial tolerance by challenge test was measured repeatedly during the course of treatment. The numbers of patients with marked improvement of bronchial tolerance (more than 75 per cent of maximum possible improvement) was 26 of 31, 19 of 21 and 9 of 28 patients treated with "A", "B," and placebo, respectively. The house dust extracts were both significantly better than placebo ($p < .01$) and bronchial tolerance changes were roughly correlated with clinical improvement from physician assessments. McAllen,[21] however, was unable to find improvement in bronchial tolerance after injections of house dust extract for a period of 12 weeks, giving apparently a much lower total dosage than that employed by Aas,[20] although comparisons of dosage are all but impossible with house dust extract.

After Spieksma et al. found that house dust samples regularly contain numerous mites of the genus Dermatophagoides (the house dust mite) and that extracts of the mite are a potent allergen in many patients sensitive to house dust,[22] Smith[23] reported on desensitization with extracts of Dermatophagoides pteronyssinus. Ten of 11 treated patients required no additional drug therapy for a period of 6 weeks after a course of injections, whereas only 5 of 11 controls could go without further treatment. Various scores of asthma symptoms were significantly better in the specifically treated group.

Immunologic responses to house dust injections were studied by May et al.[24] and indicated that commercial extracts are often of low potency and will produce measurable responses only if used in much larger doses than ordinarily employed. May's results will be described more fully in the section on immunologic responses.

Another form of "desensitization" that has been frequently employed in clinical practice is killed bacterial vaccines. Because a number of asthmatic patients have major attacks arising from or following respiratory infections and show positive skin test reactions to bacterial extracts, it has seemed reasonable to attribute symptoms to hypersensitivity to infecting bacteria. It must be pointed out that the "infective" nature of these exacerbations is supported only by clinical impressions and not by cultural and serologic evidence of the sort usually collected by investigators of respiratory infections. Furthermore, positive skin reactions to bacteria are common in patients who never have asthma. Nevertheless, a rather haphazard selection of organisms common in the mouth and throat (pneumococcus, streptococcus, staphylococcus, Neisseria, klebsiella, hemophilus, and sometimes common gram-negative bacilli) or organisms actually cultured from the mouth and throat of the individual (autogenous vaccines) have been made into vaccines and employed in desensitization regimens.

As this method has been controversial because of the conceptual difficulties described above, a number of controlled studies of various stock and autogenous vaccines in asthma have been reported. Frankland et al.,[25] Helander,[26] Johnstone,[27] Aas et al.,[28] Barr et al.,[29] and Fontana et al.[30] have reported on the use of bacterial vaccines, both autogenous vaccines and stock mixtures of respiratory organisms in a number of regimens in both childhood and adult asthmatics.

The results were almost uniformly no different from those seen in patients given placebos. Mueller and Lanz[31] claim to make a distinction between children with true infective asthma who will respond to such vaccines and children with allergic asthma who have increased difficulty during respiratory infections but do not respond to bacterial vaccine treatments. Their series, however, is not large enough to convince one that such a differentiation can be made. In any event, the evidence currently available provides no basis for the regular use of bacterial vaccines in children or adults simply because infections appear to initiate attacks.

With respect to extrinsic allergens, particularly plant pollens, relief from hay fever symptoms by adequate dosage may be considered a proven fact. Current evidence lends support to the idea that the asthmatic symptom caused by exposure to external plant pollens is relieved also although the proof is considerably less rigorous. With house dust extract several studies at least partially correlate clinical relief to increased protection on bronchial challenge, but the heterogenous nature of house dust extract and the lack of any standard for monitoring potency makes rational use almost impossible. A more rational approach would require the identification of the specific allergens in dust, testing to determine individual reactivity and treatment according to such reactivity. The use of extracts of Dermatophagoides is an advance in this direction.

It is attractive to extrapolate the positive evidence with some external allergens to others such as animal danders and molds. It is clear, however, that, where studied, clinical responses are dependent on dose and that for each extract adequate standards of potency are a necessary prelude to the establishment of the dose required for clinical improvement. The methods to do so are at hand, as will be discussed below.

As indicated earlier, inoculations for allergic manifestations have been referred to as "desensitization" or "hyposensitization" on the basis of analogy from experimentation with anaphylactically sensitive animals. While this receives some support in the demonstration that mucus membrane and skin reactivity are reduced after inoculations, Cooke et al.[5] demonstrated the development of "blocking" antibodies which specifically inhibited the passive transfer (reaginic) reaction. This is quite different from desensitization occurring in animals within minutes or hours after a series of closely spaced injections. Subsequently, Connell and Sherman[32] demonstrated that reaginic antibody as determined by titration in normal volunteers was reduced in patients who had undergone many years of inoculations. Such methods of study of immunologic responses, however, are too cumbersome and inaccurate for close study of the mechanism of action of inoculation treatment.

The development of in vitro methods for measurement of histamine release from leukocytes (principally basophils), blocking antibodies, specific reagins, and specific IgG antibodies has made it possible to study immunologic changes in some detail and to correlate these changes with clinical manifestations. To begin with, Lichtenstein et al.[33] demonstrated that the sensitivity of an untreated patient's leukocytes to ragweed antigen E correlated significantly with the severity of hay fever symptoms during natural exposure in the season of ragweed pollination. This finding has been repeated in several groups of patients with both antigen E and crude ragweed pollen extract. By the same token, in untreated patients serum levels of reagins (IgE antibodies) against ragweed correlate well with the level of basophil sensitivity as determined by histamine release, skin test sensitivity to ragweed, and severity of symptoms during the ragweed season. Lichtenstein et al. have also noted that the relationship between histamine release and symptomatology was upset when inoculations of antigen E were given to a group of patients.[33, 34] An obvious candidate for the factor producing this change was the blocking antibody described by Cooke et al.[5] Such serum antibodies can be measured accurately by their ability to block histamine release in vitro (a simple double antibody technique is now also available). Although rises in titer of blocking antibodies are related to dosage of antigen administered, as in a general way is therapeutic response, antibody titers do not account in a quantitative fashion the degree of change observed in symptom scores from the scores predicted by cell sensitivity measurement.[14, 33-35] In a general way, patients with higher blocking antibody titers fare significantly better than those with low antibody titers but the lack of a good quantitative relationship suggests that other factors are at work.[14] In a search for such factors it has been noted that in many individuals as inoculations progressed, the leukocytes have reduced or even lose entirely their ability to respond with histamine release upon exposure to specific antigen, whereas such a change rarely occurs in placebo treated individuals. The patients with complete loss of leukocyte reactivity often but not invariably fare quite well during ragweed pollen exposure. Again, the quantitative relationships are such as to suggest that still other factors are at work.[33-36]

Lichtenstein and Levy[37] noted in a group of allergic children treated with ragweed pollen extract to the point where one third of them had reduced cellular reactivity, that those patients with low or absent cellular reactivity to ragweed also had low or absent cellular reactivity to timothy pollen extract. They suggested that such "desensitization" of cellular reactivity was nonspecific and that cells from such patients might not be able to react to any antigen. A definitive study of the specificity of lowered cellular reactivity still remains to be performed. The clinical observation of Lowell and Franklin[10] that the effects of inoculation are specific has been confirmed in our clinic in a study of a group of patients sensitive to both ragweed and grass pollens. Treatment with alum-precipitated ragweed pollen extract resulted in relief of symptoms during the ragweed season but not during grass pollen season. Although good blocking antibody titers to ragweed were developed there was little or no reduction in basophil reactivity to ragweed pollen so the specificity of this change could not be studied. This study leaves open the possibility that more intensive regimens might induce non-specific reductions in cellular reactivity also.

With the development of the radio-allergo-sorbent test (RAST) a faster method for the evaluation of serum reagins (specific IgE antibodies) became available. Levy and Osler[38] had earlier shown by passive transfer to normal leukocytes that the annual natural exposure to ragweed pollen resulted in rise of specific IgE antibodies which then declined slowly during the subsequent months of non-exposure. In treated patients this annual rise was blunted. Lichtenstein et al.[39] using the RAST; confirmed this finding and noted a gradual decline in specific reagins over several years of treatment (Fig. 3). The patients with the greatest decline in reagin titer had the greatest rises in antiragweed IgG antibodies (block-

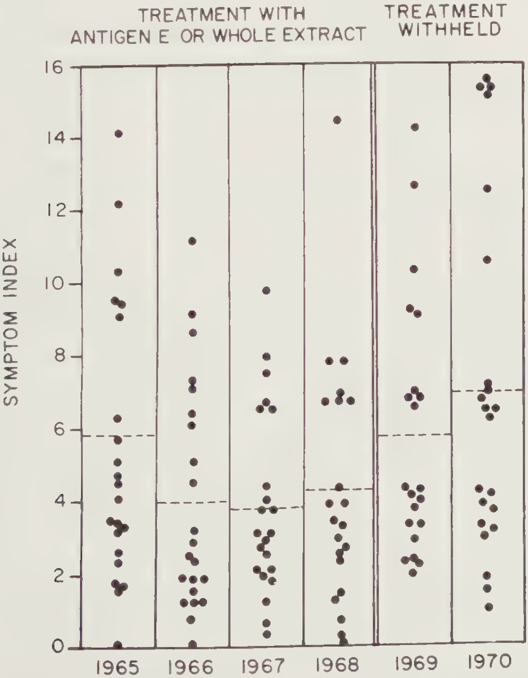


Figure 3. Average *individual* daily symptoms scores during the hay fever season in a group of patients treated for four years with ragweed antigens and then followed for two years without treatment.

ing antibodies). This should probably not be interpreted, however, as an example of feedback inhibition. The known immunologic changes that follow injection treatment with adequate dosage may be summarized as follows:

1. Titers of IgG serum antibodies which blockade specific cellular histamine release rise.
2. Titers of specific IgE antibodies fail to rise after respiratory exposure and decline slowly over months and years.
3. Basophil histamine-releasing reactivity at times declines. This change may be nonspecific and occurs despite the continued presence of circulating reagin (IgE) directed toward the allergen being employed.

These changes may not fully account for the relief in clinical symptomatology noted and other factors, immunologic or nonimmunologic, may be at play. As the known changes which result from inoculations are quite different from the concept of desensitization, we have suggested that the terms desensitization and hyposensitization be dropped and the more accurate term "immunotherapy" be employed.

It is fairly clear that adequate amounts of those protein moieties responsible for the allergenic properties of the crude allergens must be administered for both immunologic and clinical changes to occur. Not all crude allergenic materials made up for diagnosis and treatment contain such quantities of the specific allergens. For example, May et al.[24] observed the results of injection of two commercially prepared house dust extracts in dust-sensitive children. Virtually no immunologic response was observed at the doses commonly employed in practice. Relatively modest blocking antibody responses without change in leukocyte reactivity were observed only with much larger doses than those ordinarily employed. Similar findings[40] were noted with Alternaria and ragweed pollen extract.

Baer et al.[41] purchased ragweed extract from 6 different commercial houses and found a 100-fold difference in potency between the most active and least active extract in terms of skin test activity and ability to elicit basophile histamine release. Immunologic determination of antigen E content of the extracts by double diffusion in gel was shown to measure accurately the biologic potency of the extracts, whereas measurements of total protein had no relationship to biologic activity. Similar observations have been made with several related species of grass and the principal allergen of rye grass referred to as "Group I."

Development of standardization of allergenic extracts on the basis of the allergenic principle would allow dosage to be described in more rational terms. In the case of ragweed extract the studies performed in our clinic with extracts of known antigen E content indicate an accumulated annual dosage of extract equivalent to about 50 micrograms of antigen E will produce a clinically useful amelioration of symptoms. Dosage with other allergenic materials has not been similarly described. A major effort on the part of government and industry to introduce improved standards will be required to put dosage with the commonly used extracts on a rational basis.

Specialists in allergy have some index of the potency of the particular

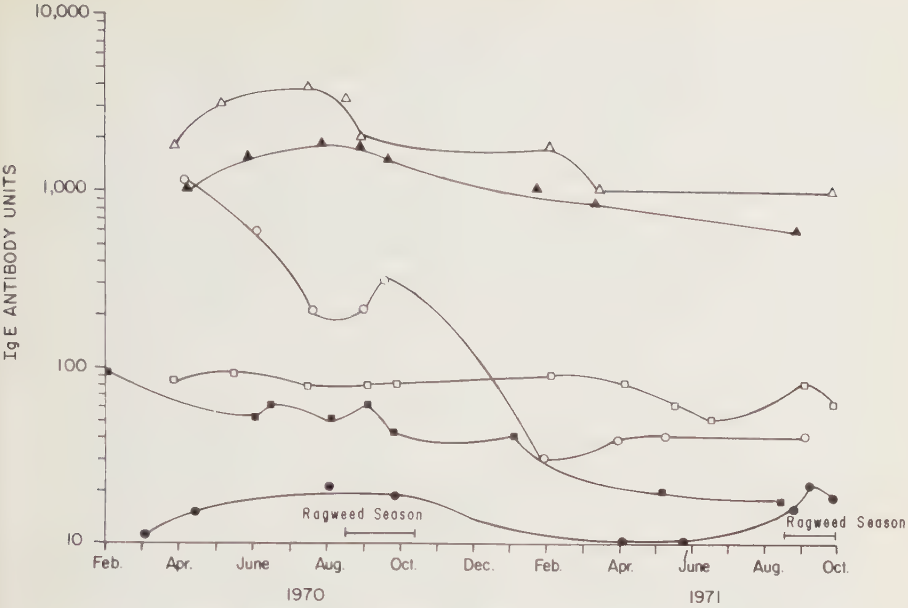


Figure 4. Specific ragweed IgE antibody titers in 6 patients undergoing ragweed immunotherapy.

extracts they employ from the reactions they observe in their patients. Dependence on these clinical observations makes use of extracts more of an art than a science but the recent scientific observations described above indicate that an underlying substratum of reproducibly observable fact does exist.The use of immunotherapy will continue to require the specialist knowledgeable in diagnosis and the intelligent use of injection treatment. An increase in scientific knowledge will only make the practice more specialized.

The general physician in referring patients to the allergist and the specialist in deciding whether to employ injection treatment will have to balance the degree of control of symptoms that can be obtained with antihistamines, decongestants and corticosteroids with the benefit to be obtained by a long, expensive, and sometimes uncomfortable program of "shots." In the case of simple hay fever, many individuals with a modest degree of sensitivity will obtain adequate control with antihistamine and decongestant medications alone. Furthermore, topically applied dexamethasone in the form of a nasal spray (Turbinaire) will achieve control of symptoms in about three-fourths of patients with straightforward seasonal disease. Immunotherapy does not invariably perform better. It should be reserved in the case of hay fever for those patients in whom simpler measures have been demonstrated not to suffice. It should be pointed out, however, that immunotherapy is the only method that provides some opportunity to modify the patient's reactivity over the long term.

Patients with multiple sensitivities and symptoms occurring in several seasons may have more reason to attempt a course of injections although there is less study of results in such patients. In asthma, one may take the attitude that it is a more serious condition and requires everything that the physician has to offer. The scientific basis for employment of desensitization in asthma, however, is less firm than it is in allergic rhinitis.

As a final statement it may be said that the methods are at hand to assess both the clinical efficacy and the immunologic mechanisms underlying immunotherapy in a greater range of allergic conditions. It is not too much to hope that further study will disclose paths to improvement in the method which will increase its usefulness in practice.[42]

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Immunotherapy

Areas of Doubt

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In accepting to take the opposite point of view to Dr. Norman concerning the possible efficacy of immunotherapy, I am reminded of the old quotation, "Twenty million Frenchmen can't be wrong." To some extent, the situation is comparable if one takes a tally of practicing allergists and asks their opinion. Almost without exception, they insist that immunotherapy is effective and there have been cries of indignation when such a view was challenged. I remember quite a few years ago, asking one of the world authorities to tell me candidly whether he thought his patients were benefited by the injections for their various forms of hay fever. Although I cannot quote him verbatim, his reply was something of the following: "I think so but I cannot be certain. If it did not help them, why would they come back year after year, spending all their good money?"

Times have changed. Where I live, patients no longer have to pay for their injections, nor indeed for their visits to the doctor, and yet the numbers are certainly increasing of those who not only insist on having injection therapy, but who will not stop it. There are many who swear to the fact that whenever they have attempted to stop, they invariably become worse. To this form of evaluation, the obvious answer is that most patients, with whatever ailment, feel better when they know something is being done for them. And yet, this cannot be the entire story. At one time it was believed that so-called 'histamine desensitization' was a reasonable form of therapy in that it was thought to induce decreased tissue reactivity to histamine. If it were simply a matter of multiple injections on a schedule not dissimilar to hyposensitization regimens with pollen extracts, this method was a natural. It also had the advantage of producing a wheal and flare locally, and with higher doses, mild systemic reactions such as flushing. However, results were disappointing and the method fell into disuse.

Over the years, there have been problems with reference to the mode of injection, the variety of schedules, and the marked variation in extracts, not to mention the innumerable factors which must be taken into consideration in evaluating the effect of immunotherapy. One of the major difficulties amongst others in the evaluation of any form of medical treatment is to be sure that one knows what one is measuring. The introduction of a new compound for the specific treatment of a metabolic disorder, where some biochemical parameter is available, and where objective signs and symptoms can be evaluated, can still leave something to be desired. When it comes to a condition like allergic rhinitis, the symptoms of which are so amenable to subjective factors, evaluation becomes exceedingly difficult. That is not to say that signs and symptoms such as lacrimation, rhinorrhea, congested nasal mucous membranes, stuffiness, and sneezing may not be present. But how can the degree of each be measured with any accuracy in a repeatable fashion? Subjective symptoms, such as itching and a miserable feeling of fullness, can only be recorded in a highly unpredictable fashion by the patient himself. How many patients have been seen who invariably state, "my symptoms always begin on August 15." Conversely, how often in a given area can one relate the sudden onset of symptoms relative to the pollen count for that particular period? Apart from these difficulties, what objective procedures can one rely on?

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Beyond doubt, the major problem when evaluating injection therapy is the unpredictability of the disease itself. For example, how severe will symptoms be in a given ragweed-sensitive patient remaining in the same area over a 5 year period? One has seen patients whose symptoms virtually disappear without therapy during one season as compared to another, without adequate explanation. It cannot be related generally to the pollen count. Many patients seem to feel worse on a "humid" as compared to a "dry" day. A rainy day is better for some than for others. It is such undefinable factors as these, in addition to others about which little is known, which make evaluation so difficult.

What about the reliability of patients' diaries? To my way of thinking, these leave much to be desired. Often times, they depend on wishful thinking, and I have seen some patients who unwittingly made statements related to convenience. For example, during a 2-year trial of repository type therapy, consisting of the usual two injections, in 1963–1964, results varied from excellent to none. The memory of those 2 years when the patients had to come to the office only twice has been recalled at times by some of whom were reverted to the usual aqueous extract multiple injection schedule. The recall consists of such statements as to how much better they were. When the chart is consulted, it is interesting to find in quite a few that, at the time, not only were the repository injections not as good as the aqueous extract injections, they were in fact virtually useless. On reminding the patient of this error in their memory, the reply is, "Oh yes, I seem to remember now that you reminded me, but it was so much more convenient than the present schedule!"

Lest there be any doubt, I am fully aware of how severe seasonal allergic rhinitis can be for some patients, knocking them out for weeks at a time. And so I believe that some means of control must be found, but as this article progresses, it will become obvious that, in my opinion, with the measurable parameters presently available, injection therapy is an unpredictable and certainly not ideal form of management. It is unfortunately the only means of "specific" therapy that we have to offer as yet.

What about those parameters which we think we know something about and can measure. Do any of these relate to the presence or absence of symptoms? Since ragweed sensitivity has been the major system to be studied, the remainder of this discussion will be confined to it. The first major advance was the definition of antigen E,[1] which permitted quantitation and seemed devoid of extraneous and, hopefully, insignificant material. All patients responding to skin testing using aqueous extracts of ragweed with a wheal and flare response reacted similarly to antigen E. Here then was a measurable antigen at last, and not only were clinical surveys made, but the material was used extensively for a large variety of basis "in vitro" studies. The clinical studies suffered from the same deficiencies as all others, namely a reliable measureable yardstick. When combined with such measurements as (1) size of wheal and flare response; (2) degree of eosinophilia either in the nasal secretions, peripheral blood or by the skin window technique; (3) secretory IgA; (4) blocking antibody (IgG); (5) serum IgE, certainly there are measurable trends, but unfortunately most of these do not relate in any clear cut manner with the presence or absence of symptoms, although they show some relation to immunotherapy.

For a time, it seemed that histamine release "in vitro" was the answer. But unfortunately even the changes produced with technique, which in the hands of Lichtenstein and his co-workers showed a change in basophil sensitivity to ragweed, and an increase in the quantity of ragweed (antigen E) required to release 50 per cent of the histamine content of the peripheral leucocytes following immunotherapy, did not correlate consistently with the clinical result.[2]

There is little doubt that a "blocking antibody" in the form of IgG is raised as a consequence of injections of pollen extracts.[3] In vitro studies show quite clearly that it has an avidity for some antigenic determinant of ragweed. It is only reasonable to expect that serial injections of water-soluble ragweed or more purified antigen E, both of which are foreign, should give rise to the formation of an antibody. However, all efforts to demonstrate some correlation between the level of blocking antibody and the presence or absence of symptoms have been unsuccessful. The more recent work of Lichtenstein would indicate that the changes occurring in basophil sensitivity are related to an increase in blocking (IgG) antibody. However, this is essentially an assumption.

What about IgE levels? Since the original and elegant definition of IgE by the Ishizakas[4] and the many studies by Johannsen and his co-workers,[5] there has arisen a considerable literature attempting to relate IgE to clinical sensitivity, and its modification by immunotherapy. The mechanisms of mediator release such as the attachment of IgE to a mast cell or basophil by its Fc fragment, the combination of allergen with the fab portion, either a single molecule, or two adjacent molecules as suggested by Stanworth,[6] the activation of enzyme systems leading to the release of mediators such as histamine, SRS-A, prostaglandins, and eosinophil chemotactic factor are now well documented.[7, 8] The role of the nucleotides such as cyclic AMP and the beta adrenergic receptors in the suppression or enhancement of the mediator release have been beautifully defined.[9] To be sure, the majority of such studies have been carried out either on peripheral white cells in vitro or on chopped lung preparations of either animal or human origin. I am unaware of any using nasal or sinus mucosa. Nevertheless, if one assumes that ragweed hay fever and asthma are more or less identical in their pathogenesis, differing primarily in the anatomic site and the presence or absence of smooth muscle, some of these parameters should be amenable to measurement in the case of the patient with allergic rhinitis.

Beginning with IgE itself, it would appear that whereas the serum level is higher than normal in patients with hay fever generally, the actual level bears no direct relation to the severity of symptoms. It is known, furthermore, that the level rises with the advent of the pollen season and then declines. It has been suggested that immunotherapy may suppress the seasonal rise in serum IgE levels.[10] This has not been confirmed in a recent carefully conducted study in which the increase in serum IgE was similar in both treated and untreated groups, and the degree of the rise was related to the preseasonal level.[11] These same workers also showed a close relationship between serum IgE and IgG levels in the group given high dose therapy, suggesting that IgG antibodies to ragweed do not suppress IgE formation. Clearly, if these results are valid, it would appear that measurements of IgE or IgG antibodies to ragweed are no index of treatment, and consequently of its efficacy. Although many studies have been made on nasal and parotid secretions in both treated and untreated ragweed-sensitive patients, no significant changes have been demonstrated in the antibody systems.[12] Similarly, studies on eosinophil counts in peripheral blood, on nasal smears, or by the skin window technique have failed to show any significant or repeatable change following immunotherapy.

Thus it must be admitted that although desensitization either with crude ragweed extract (aqueous) or antigen E can lead to a number of measurable changes such as those just enumerated, there is still no consistency in the clinical result, or its relation to these measurements. Are there perhaps some reasons why this should be?

Of all the methods of treatment for ragweed pollinosis, the most effective is elimination of the antigen. Patients who are clinically sensitive only to ragweed pollen are invariably free of symptoms on going to a ragweed-free area such as Europe or the West Coast of Canada or the United States. So long as they retain ragweed reagin, symptoms can be induced apparently on exposing them to an aerosol of ragweed extract.

Final judgment on the effectiveness of immunotherapy will depend on the development of objective – immunologic or non-immunologic – test systems; but which systems qualify? Eosinophils, or, perhaps, cyclic AMP?

First, the eosinophils. Although we take it for granted that ragweed hay fever is an immunological disease, can we in truth confine it to a humoral reaction of the so-called Type I category? Surely two other fundamental systems must be equally important. The first is delayed immune mechanisms related to T cell function. Samter who has written eloquently on the eosinophil was the first to show an eosinophilotactic factor, generated during anaphylaxis in the guinea pig.[13] And the more recent work of Kay et al.[8] has pointed up the eosinophil chemotactic factor of anaphylaxis, related to the combination of allergen with IgE fixed to a mast cell by its Fc portion. Whatever its function may be, and there are many possibilities, the eosinophil seems to be a fundamental factor in the allergic response. Following on the work of Basten et al.[14,15] who showed that a viable T cell population is essential before one can obtain an eosinophilia, Colley[16] has demonstrated that stimulation of sensitized T cells in vitro either with specific antigen or PHA release a very potent eosinophil stimulation promoter. This is perhaps the closest relationship between cell mediated immunity and the atopic state, if we accept the assumption that the eosinophil is fundamental to the allergic reaction. There are also the observations of Brostoff and Roitt[17] concerning the microscopic appearance of a skin test site at 48 hours when an antihistamine is injected into the site prior to the injection of an allergic extract. They described the cells as being mononuclear and closely resembling those found in the tuberculin reaction.

The second system is cyclic AMP which at least in in vitro studies exerts a major controlling effect on the release of chemical mediators. In a recent article, Parker and Smith[19] have shown a close relation between the level of cellular cyclic AMP in peripheral lymphocytes and the severity of bronchial asthma. In the severe asthmatic, the level is low and does not respond to isoproterenol. The mild asthmatic on the other hand has a level closer to normal, and following the addition of isoproterenol, there is a substantial rise in this nucleotide. It is not entirely clear as to whether these changes in cyclic AMP levels relate to T or B lymphocytes, or perhaps both. There is a suggestion that B cells are involved primarily, but further studies will be necessary to clarify this point. In any case, these interesting findings seem to be more impressive than any previous reports as an in vitro test which correlates well with the severity of symptoms insofar as asthma is concerned.

If we believe that rhinitis on the one hand and asthma on the other are manifestations of the same disease process but in different anatomic locations, measurements of cyclic AMP in peripheral lymphocytes might be a better parameter for the monitoring of symptoms in the former.

As to ragweed hay fever and the whole question of immunotherapy, the subject must be re-evaluated in terms of the newer and different ragweed allergens. For, in addition to antigen E, Goodfriend[20,21] has described Ra3 and Ra5. Ra5 is a low molecular weight (4900) pure antigen of ragweed. The aminoacid residues have been determined, and the structure is presently being elaborated. It is highly active biologically in a selective manner. It is interesting that Ra5 which has recently been investigated by Marsh et al.[22] reacts in only 17 per cent of subjects who are clinically sensitive to ragweed, and give a strong reaction of the wheal and flare type both to whole ragweed extract and to antigen E. There is continuing evidence that this may be related to HLA antigens of the HL-A7 cross-reacting grouping. More recent evidence points to a similar circumstance with Ra3. It should be pointed out that these are separate antigens, and not antigenic determinants on a large ragweed molecule. These highly biologically active antigens are of quite low molecular weight and now available in pure form. The present trend would seem to indicate at best that not all ragweed rhinitis patients are alike. Some are sensitive to one moiety such as Ra5 and others to Ra3. If this sensitivity is related to the presence of so-called IR genes,[23] and both the evidence of Marsh et al. and Levine[24] support this, a more precise approach to therapy would seem to be indicated.

Finally, it seems to me that IgE and eosinophil are good things to have. I base this on the work of Bloch[25] with reference to parasitic infestation, in an animal model, and the observations of Phills et al.[26] in humans who had ingested Ascaris suum which is related to Ascaris lumbricoides. Apparently, getting rid of the parasite seems to be dependent on high levels of IgE and eosinophils. This probably cannot be directly compared with ragweed pollinosis, where it appears that suppression of IgE antibody to ragweed might be an effective means of therapy. So far, there is little evidence that immunotherapy accomplishes this. On the other hand, we may be doing something about which we are unaware as yet, and I would suspect that immunotherapy as presently practiced might still be a good thing, which really means that I suspect it works, but adequate proof is still lacking.

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Symptomatic Treatment of Adults with Bronchial Asthma

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Bronchial asthma, a common disease, is satisfying for the physician to treat. Since the airways obstruction of bronchial asthma is defined pathophysiologically as *reversible*, the goal in treatment is opening the airways and maintaining their patency. Continuing disability should not be acceptable in a patient with asthma.

The treatment of bronchial asthma has improved considerably over the past fifty years. In his *Principles and Practice of Medicine*, Osler recommended remedies which, with the exception of potassium iodide, sound quaint or atrocious today.[20] Permanent cures were said to be occasionally produced by chloroform and combinations of morphine and strychnine. The reader wonders what was meant by "permanent." Morphine continued to be recommended in the Eleventh Edition in 1931, despite Salter's beautifully reasoned advice against the use of opium in patients with asthma in 1860.[26] "Sedative antispasmodics," including belladonna, henbane, stramonium, and lobelia, were recommended in solution or as cigarettes along with nitrate of potash paper. Tobacco smoke was thought to be almost as good. Cauterization of the mucous membranes of the nose was said to give great relief, particularly in patients with swelling and irritation. One wonders how many normal noses were cauterized on Osler's authority. Osler's critical sense is exemplified in a remark of his about Thomas Willis' *Pharmaceutica Rationale:* "It is as dead as Willis. It gives me shudder to think of the constitution our ancestors had, and how they withstood the assaults of the apothecary."[17] It gives me shudder to think how asthmatics have been mistreated by physicians throughout the years, including Sir William himself. It gives me pause to think how quaint or atrocious our recommendations may seem to physicians 50 years from now.

Bronchial asthma is an extremely variable disease, and treatment must be fitted to the needs of the individual patient. Correct diagnosis is vital, and accurate classification of asthma as extrinsic or intrinsic, seasonal or perennial, acute-intermittent or chronic is helpful in planning a successful course of treatment. The pathophysiology of asthma involves bronchospasm in mild asthma, and progressive airways obstruction from mucosal edema and mucous plugging in the severe asthmatic. The patient with mild asthma responds to simple measures whereas the severe asthmatic may require heroic treatment. The subsequent discussion will progress from the simple symptomatic treatment of the mild asthmatic to the more complicated treatment of the severely ill asthmatic patient.

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GENERAL MEASURES

Environmental Control

Osler, in the First Edition of his textbook, recommended 6 month periods in Florida or southern California, and in the Eighth Edition added the observation that Egypt is a peculiarly satisfactory winter climate for the asthmatic.[20] Although a rare patient may appreciate such advice, most would find the carrying out of these recommendations disruptive if not impossible.

Patients with allergy to seasonal pollens will be relieved if these pollens are avoided. Ragweed can be escaped west of the Rockies or anywhere outside North America, and vacations may be planned accordingly by some patients. Environmental control can be practiced in any locality by the patient's staying inside, excluding pollen by tightly closed windows and doors, with the temperature made tolerable by recirculating inside air by means of an air conditioner. Avoidance of house dust requires different measures, and molds are more difficult to escape.

Patients with nonallergic asthma are rarely benefited significantly by a change in geographic location. Disruption of family and job is frequently a practical deterrent to this recommendation as well.

Support and Reassurance

Patients with bronchial asthma need to have the disease explained and the expected course discussed. As with any chronic disease, which in this case may be simply annoying or recurrently disabling, the continuing support and availability of the informed primary physician is an essential part of optimal care. Prompt treatment of severe attacks and periodic check-ups of the patient with asthma establish confidence in and rapport with the physician which is an important part of any therapeutic relationship. Formal psychotherapy and the use of tranquilizers have no place in the treatment of bronchial asthma per se, but may of course be indicated for co-existing problems as in any patient.

Since bronchial asthma is reversible, and many patients reach a stage of having less trouble as they get older, an aura of optimism is realistic and should be fostered by the physician.

SYMPTOMATIC TREATMENT ACCORDING TO SEVERITY

Mild, Intermittent, Acute Attacks

The typical patient with *mild* asthma, usually of the extrinsic or allergic type, experiences acute paroxysms of wheezing dyspnea with cough. These attacks frequently occur in the evening or night and are not effort-related. A seasonal history may be obtained. Between attacks the patient seems clinically normal.

These attacks can usually be successfully treated by the patient himself with *bronchodilators* administered orally or by inhalation. Packaged combinations of ephedrine and aminophylline with a mild sedative to counteract the excitation produced by ephedrine are convenient and economical. Recent advances in understanding the effects of sympathomimetic agents on the cyclic AMP system make ephedrine-aminophylline combinations rational.[2, 8, 13, 21] Pushing theophylline to tolerance may occasionally be useful in patients failing to respond to combination tablets. Anorexia or nausea is usually the first toxic symptom. Several forms of theophylline are available including aminophylline, oxtriphylline, elixir, suppository, and aqueous rectal solution. An occasional patient with aspirin sensitivity may react adversely to tartrazine yellow No. 5, a dye found in some colored tablets.[4, 11]

Oral bronchodilators produce a sustained effect but require 15 to 45 minutes to work. Many patients prefer an inhaler containing isoproterenol for quick relief. Inhalers are very useful and quite safe if employed for rapid relief of an occasional acute attack. Problems may arise with overuse in chronic asthma.

Since mild, intermittent, acute attacks of asthma are caused by simple bronchospasm, the patient's use of bronchodilators alone should suffice in treatment. Occasionally they fail.

Acute Bronchial Asthma Unresponsive to Patient-Administered Bronchodilators

The patient who has developed an acute attack of asthma resistant to his own treatment efforts will usually seek the help of a physician. An acute attack in this sense has begun a few hours before in a patient previously stable. Complicating factors such as infection or excessive allergen exposure may be responsible and should be sought.

Our initial treatment regimen in a patient of this type is to give aminophylline intravenously, 250 to 500 mg. over a 5 to 10 minute period, carefully timed to prevent too rapid administration. Twenty to 30 minutes later, 0.3 to 0.5 cc. of aqueous epinephrine 1:1000 is given subcutaneously. Intravenous epinephrine is not recommended because of the possible risk of cardiac arrhythmias. A good response usually occurs within 30 to 60 minutes, at which time the patient is instructed to take regular oral bronchodilators for a few days and report back to the physician if he experiences any further difficulty.

If the patient fails to respond to this regimen, and has significant continued or increasing difficulty, by definition he has status asthmaticus and should be hospitalized for more intensive treatment (see below).

Chronic Bronchial Asthma

Asthmatic patients whose airways obstruction is relieved incompletely by the use of oral bronchodilators may put up with partial disability for weeks or months. Objective measurement of pulmonary function, such as maximum expiratory flow rate (MEFR), forced expiratory volume in one second (FEV_1), and vital capacity (VC) are invaluable aids in properly evaluating and following these patients. When continued disabling but nonprogressive bronchial obstruction occurs in this way, chronic asthma (not status asthmaticus) is the proper diagnosis, and a revision of the therapeutic regimen is indicated.

Reversibility of airways obstruction in a chronic asthmatic may not be easily achieved by simple measures such as an injection of epinephrine or inhalation of isoproterenol. Such a failure to respond commonly leads to a misconception that the patient has an irreversible type of chronic obstructive lung disease (that is, emphysema or chronic bronchitis). A trial of steroids may be necessary in many patients to evaluate the possibility of reversibility, with consequent prognostic and therapeutic implications.

In chronic asthma the first approach is to evaluate the current treatment program. Oral *bronchodilators* should be used regularly in optimal dosage to achieve therapeutic benefit without bothersome side effects. Aminophylline, 200 mg. every 6 hours, may be added to the current program, and subsequently increased at weekly intervals by 100 mg. every six hours until satisfactory therapeutic results or toxicity occurs.[10] The common toxic symptoms of anorexia, nausea, and vomiting are related to serum levels and dictate a decrease in maintenance dosage. *Expectorants* should be tried, since some patients find saturated solution of potassium iodide (SSKI) or glyceryl guaiacolate very helpful in facilitating the raising of mucus. SSKI is begun in low doses, 5 drops 3 times a day in a glass of juice or other liquid, and increased weekly by 2 or 3 drops until a maximum of 15 drops three times a day is reached, unless side effects are encountered sooner. Acne is dose related. Prolonged continuous use has been rarely associated with myxedema, so patients are advised to use SSKI 3 weeks a month or 5 days a week to provide periodic interruption of iodide therapy. If the patient notices no benefit from iodide therapy within a few weeks, its use is discontinued. SSKI should not be used during pregnancy because of hazards to the fetal thyroid.

Frequent use of inhalers should be discouraged in the chronic asthmatic because of drying effects and diminishing effectiveness. A rare patient may experience bronchoconstriction following overuse of isoproterenol and must not interpret this as indication for increased use. The proper use of an inhaler is for occasional acute exacerbations when quick relief is needed. If the patient is using his inhaler more often than 4 to 6 times a day, other treatment should be added. Asthma mortality associated with the overuse of inhalers has been variously ascribed to overdosage, particularly with the use of an increased concentration of isoproterenol now withdrawn from the European market where it was associated with an increased incidence of asthma deaths, to the fluorocarbon propellant, to the development of tolerance, or to an idiosyncrasy. The most likely explanation is the continued overuse of an increasingly less effective agent in a patient with relentlessly progressive asthma.

Antibiotics, such as tetracycline, are indicated for episodes of purulent bronchitis.

If a chronic asthmatic continues to be disabled with documented bronchial obstruction (MEFR consistently below 100 liters per minute) despite optimal use of bronchodilators, expectorants, and antibiotics, *corticosteroid* therapy is warranted unless contraindicated because of co-existing diseases.

Once indications for corticosteroids are established, our routine is to apply an intermediate PPD (unless the reaction is known to be positive) and re-examine the chest x-ray. If there is immunologic or radiologic evidence of prior experience with tuberculosis, isoniazid, 300 mg. daily, is given concurrently with corticosteroids.

Prednisone is our corticosteroid of choice,[23, 28] unless fluid retention is a significant problem, in which case a fluorosynthetic glucocorticoid is used. We usually begin prednisone in a dosage of 60 mg. a day for 1 to 2 weeks depending on initial severity and the early response. We then taper by 5 mg. a day until 20 mg. a day is reached. This level is maintained for 1 to 2 weeks, and at that point gradual tapering is begun by 2.5 to 5 mg. steps at 1 to 2 week intervals. The patient is monitored regularly with objective pulmonary function tests (e.g., VC and MEFR). The tapering is continued until the patient is off prednisone completely or has a recurrence of symptoms and obstruction. In the latter event, the corticosteroid is resumed, often at the initial dose level, and tapered again to the necessary maintenance level. After a few months, another attempt may be made to taper off very gradually if the patient is doing well. In the elderly patient discontinuation of corticosteroids after prolonged treatment may be dangerous, and should be undertaken with close observation if at all.

The therapeutic response of the asthmatic patient to corticosteroids is predictable. Symptomatic and subjective improvement will usually occur within a few days, auscultatory abnormalities clear a little later, and mucus production gradually lessens and disappears in most patients by 1 or 2 weeks. Objective measurements of bronchial obstruction (MEFR, FEV_1) are the last to return to normal, often requiring 2 to 6 weeks for maximum reversibility to be achieved. These facts have several important implications: (1) The physician may be misled by subjective and auscultatory findings into considering the patient well, and may taper off the steroids too rapidly; this usually results in a recurrence of severe asthma within two weeks. (2) If a therapeutic trial of steroids is being given to test extent of reversibility, testing too soon may lead to an erroneous diagnosis of irreversible airways obstruction. (3) Proper evaluation of the therapeutic response in asthma (and other obstructive lung diseases) requires periodic measurement of pulmonary function. Relatively inexpensive equipment is available for rapid and convenient measurement of vital capacity, maximum expiratory flow rate and timed forced expiratory volume.

With prolonged use of corticosteroids, side effects may be decreased by using one dose in the morning rather than divided throughout the 24 hour period, which is more effective therapeutically. Attempts to switch patients to prednisone administered every other day, as recommended by others,[5, 7, 29] have consistently failed in our hands except as a penultimate maneuver in patients able to gradually discontinue steroids. Patients requiring maintenance steroids to prevent progressive disability have not found 1 dose every 48 hours satisfactory therapeutically. The use of commercially available inhalational corticosteroids has been disappointing. The best way to avoid steroid side effects is to avoid steroids; if steroids are required, the primary goal is functional rehabilitation of the patient rather than avoidance of side effects. Asthma patients in general tolerate steroids quite well.[14] The average maintenance dose in steroid-dependent asthmatics is approximately 10 mg. of prednisone daily.

Some patients are found to be relatively resistant to corticosteroids. This has been anticipated by observing the effect of a test dose of cortisol on the eosinophil count.[27] Occasionally, steroid resistance may be explained by the effect of other drugs, notably phenobarbital, on steroid catabolism by the liver.[3]

The role (or possible role) of immunotherapy in the control of respiratory allergies has been discussed, in detail, in other contributions to this symposium.

A cause and effect relationship between sinusitis or, for that matter, between infected teeth and bronchial asthma has never been clearly established, but infected sinuses or infected teeth of asthmatics might require medical attention. Other "foci of infection" are chiefly of historical interest.

Status Asthmaticus

Severe airways obstruction in an acutely dyspneic and ill asthmatic which does not respond to the optimal administration of aminophylline and epinephrine (see above) defines status asthmaticus. This differs from chronic asthma, which may also respond poorly to acute administration of bronchodilators, in that status asthmaticus is an acute progressive event in which the patient is anxiously seeking relief from severe dyspnea at rest. Chronic asthma is relatively stable and is tolerated by the patient even though he may have significant functional disability.

Status asthmaticus is a life-threatening medical emergency which requires prompt treatment. Mucosal edema and particularly mucous plugs are important pathologic features of status asthmaticus and explain resistance to bronchodilators and the slow therapeutic response. Bronchial smooth muscle may be resistant to sympathomimetic agents because of factors resulting in beta-adrenergic blockade, such as acidosis. These factors can be pharmacologically attacked,[18] but the physician cannot count on therapeutic success with this approach alone.

Our recommendations for the treatment of status asthmaticus include the following:

1. Carry out a quick history and physical examination to verify the diagnosis and locate complications, such as infection or pneumothorax. The patient has presumably been evaluated before receiving aminophylline and epinephrine to establish the diagnosis of status asthmaticus, in which case this step has already been performed. Complete blood count, urinalysis, sputum culture, electrolytes, and chest x-ray examination should be done as soon as practical.

2. Intravenous fluids (5 per cent dextrose in water) should be started, which allow administration of intravenous drugs as needed and beginning hydration of the patient.

3. Obtain arterial Po_2, Pco_2, and pH measurements. Give oxygen if

patient is cyanotic. Blood gases will help determine need for oxygen therapy and the severity of respiratory failure. Progression of hypoxia, hypercapnia, and/or patient fatigue may require treatment by intubation and mechanical ventilation.

4. Hydrocortisone (or equivalent soluble steroid suitable for intravenous use) should be given immediately intravenously, 100 to 300 mg. This will not help the patient for 12 to 48 hours, so the sooner begun, the better. The need for continued administration will be decided by the subsequent course.

5. Avoid sedation. The patient's anxiety will clear when the airways open, and meanwhile he needs to work hard to breathe. Sedation may result in apnea.

6. Assess response to previously administered aminophylline and epinephrine and plan a regular schedule of administration of these agents. Aminophylline, 500 mg., should be given over a 10 minute period as IV push, followed in 30 minutes by 0.3 to 0.5 ml. of epinephrine subcutaneously. Repeat both every 6 to 8 hours. Discontinue if there is no apparent benefit. Continuous drip aminophylline is empirically less effective initially than a timed bolus, but may be used as an adjunct to the bolus to maintain blood levels. Do not push aminophylline beyond the point of nausea.

7. Repeatedly assess the degree of respiratory distress subjectively and objectively with blood gases. Ventilatory measurements are unreliable, unnecessary and a cruelty to the patient until some improvement occurs. Hypoxemia may increase following initial therapy despite a significant decrease in airways obstruction, but this is rarely serious. If the patient is improving, keep up the program, repeat hydrocortisone, 100 to 200 mg. IV every 6 hours, until the patient can take oral prednisone, 15 mg. every 6 hours. If symptoms and findings rapidly abate over the first few hours, continuation of steroids may not be necessary (unless the patient has been treated recently with steroids). If the patient is losing or at least not gaining, several other considerations are appropriate:

a. Antibiotic treatment empirically. History of drug allergy should be carefully sought.

b. Intermittent positive pressure breathing with nebulized isoproterenol and saline may be helpful in raising secretions and thereby improving ventilation. Mucous plugs may be loosened by this means, an important step in reversing the process. If the machine appears not to be helpful or upsets the patient, its use should not be demanded. After the acute phase is over, nebulized bronchodilators and vapor can be administered as effectively and much less expensively by simpler apparatus. IPPD machine treatment is extravagant and of no proved value to the ambulatory asthmatic.

c. Intubation and mechanical ventilation is indicated for increasing hypercapnia with or without hypoxia (which should be correctable by oxygen therapy) particularly in a fatigued patient. P_{CO_2} is a very important prognosticator in status asthmaticus.[21] Early in the severe attack the P_{CO_2} is often low (20 to 25 mm. Hg); as it approaches normal (despite continuing dyspnea) the physician should be increasingly concerned about the patient's ability to continue the work of breathing. When the P_{CO_2}

exceeds 45 mm. Hg, intubation and mechanical ventilation are usually indicated. With intubation and mechanical ventilation, the rule against sedation no longer holds and may be essential to coordinate the patient's respiratory efforts with the ventilator. For effective mechanical ventilation the patient's shallow rate of 30 to 40 per minute may need to be reduced to 6 to 10 per minute to achieve adequate emptying of the lung in the expiratory phase, which is greatly prolonged in airways obstruction. Even with mechanical ventilation the expiratory phase is dependent on the elastic recoil of the lung and not on any function of the machine. The use of sedatives or muscle relaxants requires vigilant monitoring since mechanical failure may leave the patient apneic.

d. Sodium bicarbonate may be useful in patients whose acidosis is not responding to mechanical ventilation but should rarely be necessary. Occasionally, relief of bronchospasm appears expedited by the correction of acidemia, perhaps by increasing epinephrine responsiveness. The administration of 90 mEq. (100 ml. of 0.9 *M* solution) of sodium bicarbonate intravenously over a 5 minute period has been recommended, followed by repeat blood gas measurements and readministration of sodium bicarbonate similarly at 10 minute intervals until the acidemia is adequately corrected.[18] If the patient is simultaneously being ventilated, with lowering of the P_{CO_2}, overcorrection of the acidosis must be guarded against, since alkalosis may lead to hypotension, fits, coma, and cardiac arrest.[12]

8. Secretions should be kept cleared by whatever means is necessary, including suction in the fatigued or intubated patient. Fluid intake should be adequate to correct dehydration and to maintain a good urine output of around 50 cc. per hour. Fiberoptic bronchoscopy and bronchial washing with normal saline may be useful in removing tenacious mucous plugs in extreme situations or in lobar or segmental obstruction. This procedure can be carried out without interrupting assisted ventilation.[25]

9. Corticosteroids ordinarily begin to be effective 24 to 48 hours after institution of therapy, sometimes later. Time is on the patient's side, assuming that ventilation is maintained. Gradual improvement is expected and subsequent steroid treatment is similar to that described for the chronic asthmatic. Oral bronchodilators and expectorants are used as needed.

10. Subsequent management of the patient who has recovered from status asthmaticus depends on whether he has chronic asthma or acute intermittent asthma as discussed above.

11. Tranquilizers and psychotherapy have no role in the treatment of status asthmaticus, but may be helpful subsequently in occasional patients who have psychogenic factors adding to their illness, as in any other disease. Treatment of asthma with placebos should be condemned.

ADDITIONAL THERAPEUTIC MEASURES

Most of the means of treatment in bronchial asthma have been covered in other sections. These include: (1) bronchodilators (oral and inhalational), (2) expectorants and hydration, (3) antibiotics, (4) corticosteroids, (5) mechanical ventilation and (6) specific desensitization. In this section we discuss methods in current use which are of doubtful value, and newer methods which show promise.

Current Treatment Methods of Doubtful Value

Certain methods in this category have been mentioned in passing in the preceding section. These include tranquilizers, formal psychotherapy, and IPPB.

FOOD ELIMINATION DIETS. Asthma has been treated since Greek times with various diets, despite which there is no factual evidence that "chronic masked food allergy" has anything to do with asthma in adults.[16, 22] On the other hand, occasional patients do have exquisite allergy, manifested occasionally as asthma, following ingestion of certain foods, among which nuts, seafood and eggs are prime offenders. Food additives and preservatives may rarely provoke an asthma attack. Aspirin-sensitive patients may uncommonly react similarly to tartrazine yellow dye present as coloring in many foodstuffs and medicaments.[4, 11]

Questionable techniques based on supposed subtle food allergy are unfortunately being rather widely taught, particularly by otolaryngologists and pediatricians. These include provocative-neutralizing methods, in vitro cytotoxic food tests and sublingual challenge with food extracts. These procedures require controlled studies to establish validity and these are wanting. The literature on these procedures is vanishingly small, and what exists is largely anecdotal reportage. A controlled study by a Committee on Food Allergy, Research Council, American Academy of Allergy, failed to demonstrate any benefit to asthmatics with a rigid elimination diet.[30]

REMEDIES AND NOSTRUMS. *Small Doses of Corticosteroids.* Several proprietary drug combinations contain small amounts of a corticosteroid. "Dose packs" are sold for quick tapering of steroids over a few days. Depot intramuscular steroid preparations produce uncertain dose levels of irregular duration. These preparations may appear beneficial in mild seasonal asthma, but when a disabled patient resistant to other measures requires corticosteroids it is preferable to begin with full doses as described above under chronic asthma.

Antihistamines. Antihistamines are drying and have no demonstrable beneficial effect in bronchial asthma.

Diethylcarbamazine (Hetrazan). Early reports suggested that diethylcarbamazine, an antihelminthic, was helpful in the treatment of bronchial asthma, and subsequent studies demonstrated that diethylcarbamazine selectively inhibited the release of slow-reacting substance of anaphylaxis (SRS-A) in the rat.[19] Clinical trials in human asthma so far have failed to substantiate earlier claims of benefit.

Therapeutic Agents of Promise

Several new drugs have been used clinically in other countries, but have not been commercially available in the United States. A brief discussion of the more important of these follows.

DISODIUM CROMOGLYCATE (CROMOLYN SODIUM). Cromolyn sodium is inhaled as a dry powder and has been shown to selectively inhibit the release of histamine from rat mast cells.[19] Clinical trials have demonstrated improvement in some asthma patients following regular administration.[1, 15] This agent is not useful for treatment of an acute attack. Significant toxic effects have not been reported. Cromolyn sodium became commercially available in this country in June 1973.

BECLOMETHASONE DIPROPRIONATE AEROSOL. Aerosolized corticosteroids in bronchial asthma have been disappointing, in contrast to their effectiveness in controlling nasal allergy. Beclomethasone, a new topical steroid in use in England, has been reported to be quite effective in treating bronchial asthma as an adjunct to or replacement for systemic steroids, and to have negligible systemic steroid effects.[6]

ADRENERGIC BETA-2 STIMULATORS. Sympathomimetics have been used in the treatment of bronchial asthma for centuries and have included ephedrine, epinephrine, and isoproterenol. The separation of adrenergic receptors into alpha and beta types, with beta receptor stimulation resulting in bronchodilatation, led to recognition of specific beta stimulators. Isoproterenol is the prime example of a beta adrenergic stimulator.

A recent advance in this area is distinction between beta-1 and beta-2 receptors, stimulators, and blocking agents. Stimulation of beta-1 receptors (myocardium) causes increased cardiac output; beta-2 receptor stimulation (bronchial smooth muscle) causes bronchodilatation. Isoproterenol stimulates both beta-1 and beta-2 receptors, whereas certain other drugs, of which salbutamol is an example,[9] selectively stimulate beta-2 receptors. Thus, bronchodilatation can reportedly be achieved without cardiac side effects. Further studies of specific beta-2 stimulators in the treatment of asthma are awaited with interest.

CONCLUSIONS

Bronchial asthma is a reversible disorder, and appropriate management requires careful assessment of each individual patient. Significant disability from bronchial asthma should not be expected or readily accepted by either the patient or his physician.

Treatment is effective and ranges from simple bronchodilators to intubation and mechanical ventilation. Some measures used in the past are not acceptable and some therapeutic techniques in current use are unproved. Certain newer agents show promise in the treatment of asthma.

Elucidation of pathogenetic mechanisms has led to improved methods of treatment. Much more needs to be learned before bronchial asthma can be considered conquered, certainly, but current treatment methods are sufficiently successful that the patient with bronchial asthma and his physician can with justification be optimistic about the future.

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Allergic Emergencies

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Allergic emergencies are the result of the release of chemical mediators secondary to an immunological reaction. The clinical conditions so mediated and threatening life are anaphylaxis and laryngeal edema. Other emergencies which occur in allergy are due to a combination of immunologic and nonimmunologic factors. Status asthmaticus is an example. These are discussed elsewhere in this symposium.

The clinical course of anaphylaxis and acute laryngeal edema is so dramatic that it is surprising that their pathogenesis is not always clear. It is the objective of this review to examine the pathophysiologic pathways, to define the common substances which might precipitate these conditions, and to stress prevention, which is as important as—if not more important than—therapy. This is especially true since many of the episodes of anaphylaxis and acute laryngeal edema will occur at some distance from a medical treatment facility. This discussion will be confined to systemic anaphylaxis, although the mechanism for the production of local anaphylaxis (urticaria or angioedema) is quite the same.

Susceptibility

Why certain individuals are susceptible to these types of reaction is unknown. Whether the existence of other allergic problems constitutes a predisposition to anaphylactic reaction remains unclear.[2] The evidence for or against a predisposing role of atopy is not yet persuasive, and one of the more recent studies negates the relationship.[3]

Signs and Symptoms

Ths signs and symptoms associated with anaphylaxis usually occur within seconds to minutes after exposure to the precipitating agent. The first manifestations may involve the skin, with diffuse erythema, a sense of warmth, and the development of generalized urticaria. This is often followed by severe and rapidly progressive respiratory distress caused by

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bronchospasm and/or angioedema involving the larynx. Gastrointestinal symptoms may include vomiting, abdominal cramps (sometimes resembling menstrual cramps or labor pains), and diarrhea, which may occasionally be bloody. Vascular collapse may occur, rapidly following the dermal-respiratory complex of symptoms, or without preceding respiratory distress.

Pathology

James and Austen reported that severe respiratory distress or profound shock with or without respiratory difficulty was commonly encountered preceding fatal anaphylactic reactions.[4, 5] They summarized numerous reports of pathologic findings in anaphylactic death. The descriptions included acute pulmonary emphysema, laryngeal edema, and in fatal cases without significant respiratory difficulty, either visceral congestion or no significant anatomic findings. These authors studied 6 fatal cases: 5 of these patients had acute laryngeal edema or pulmonary emphysema or both; neither was present in the sixth case. The interval between parenteral administration of antigen and death ranged from 16 to 120 minutes (penicillin in 3 patients, and, in 1 patient each, guinea pig hemoglobin as a skin test in a volunteer, bee venom, and ragweed extract.)

The predominant pathologic abnormality was in the respiratory system of 5 patients, 4 of whom had severe edema of the upper respiratory tract, including the hypopharynx, epiglottis, larynx, and trachea. Two of the patients with laryngeal edema, and the fifth patient with respiratory symptoms, had acute pulmonary hyperinflation which was presumably due to outflow obstruction in the upper respiratory tract. The sixth patient suffered pain and shock without respiratory distress, and the postmortem examination did not reveal the cause of death. There were increased numbers of eosinophils in the sinusoids of the spleen and liver, the lamina propria of the upper respiratory tract, and the pulmonary vessels in several patients.

Pathogenesis

Anaphylaxis occurs when an antigen, normally innocuous to animal or man, reacts with an antibody and triggers a series of pathologic events. This antigen-antibody interaction results in increased capillary permeability and contraction of smooth muscle in certain organ systems often unique to individual animal species.[6] The organ systems involved in each experimental animal or in man determine the clinical course.

In the guinea pig, the primary organ is the smooth muscle of the bronchi, which constricts, leading to dyspnea, hypoxia, and death.[7, 8] Pulmonary artery constriction with right heart failure is the primary cause of death in anaphylaxis induced in rabbits.[9, 10] The primary shock tissue in the dog is the venous system of the liver which contracts causing severe hepatic congestion.[11, 12] Organ systems involved vary from species to species. Factors which determine the "shock organ" include variations in the immune response; location of smooth muscle; and distribution, sensitivity to, and rate of degradation of the chemical mediators. In man, the lungs and the vascular system are affected.[4] Main symptoms include severe respiratory distress, laryngeal edema, and circulatory collapse.

The immune mechanism responsible for anaphylaxis in man has been well characterized during the past decade. Substances such as penicillin, pollen, and horse serum, which are well tolerated by most individuals, induce in certain persons the synthesis of a specific antibody, previously referred to as reagin or skin-sensitizing antibody and now known to be IgE immunoglobulin. This antibody is homocytotropic; i.e., it is capable of attaching to cell surfaces. The most important cell surface to which it attaches appears to be the human mast cell. Thus, this type of anaphylaxis has been referred to by Becker and Austen as *cytotropic antibody-induced anaphylaxis*[13] and accounts for most anaphylaxis seen in man. Upon rechallenge, an antigen-antibody interaction on the mast cell surface acts as a catalyst for the release of various chemical mediators in the human target organ systems.

The chemical mediating substances which appear to play a role in human anaphylaxis include histamine and slow-reacting substance of anaphylaxis (SRS-A).[14] Other equally or more important undiscovered chemical mediators most likely exist.[15] However, the two chemicals mentioned above are the only substances which have been substantially implicated by available in vitro and in vivo experimental studies.

Histamine, which is found in greatest concentrations in mast cell granules, increases capillary permeability, contracts bronchiolar smooth muscle, and stimulates exocrine gland secretion in human beings. SRS-A, an acidic lipid, may also play a role in human anaphylaxis. Passively sensitized human lung tissue with serum containing IgE releases this lipid substance upon antigenic challenge. Isolated human smooth muscle preparation from the lung also is contracted by SRS-A.[16] In spite of these in vitro experiments, more conclusive evidence is needed before it can be unequivocally stated that SRS-A plays a role in human anaphylaxis. Both kinins and serotonin have been implicated as being important in animal anaphylaxis. Experimental evidence for their role in human anaphylaxis remains inconclusive.[14]

Becker and Austen have alluded to three other mechanisms which result in anaphylaxis.[13] *Aggregate anaphylaxis*, which also probably occurs as a result of a secondary release of chemical mediators, does not involve a latent period of sensitization. Rabbit anti-rat gamma globulin injected intravenously into rats reacts with rat gamma globulin and produces anaphylaxis.[17]

Aggregated human gamma globulin can also cause anaphylaxis, possibly through complement activation and subsequent release of anaphylatoxin.[18] The exact mechanism for this reaction remains unclear. It is likely that several different mechanisms are involved in various experimental and clinical situations.

A third type of reaction described by Becker and Austen is *cytotoxic anaphylaxis*, where damage is imparted directly to the cell wall, with which the antibody reacts.[13] Complement is required for this type of reaction, an example of which would be an acute hemolytic transfusion reaction.

Finally, *protracted anaphylaxis* is defined by Becker and Austen[13] as anaphylaxis occurring slowly, manifested experimentally in guinea pigs by hypotension, hypothermia, and irreversible shock. This series of events occurs in sensitized animals injected with antigen intraperitoneally, subcutaneously, or while protected by intravenous antihistamines. The human prototype would be the continuation of signs of a systemic reaction after the pharmacologic substances to treat the reaction have been degraded.

A fifth category should also be included, i.e., *anaphylactoid reactions*. These can be defined as systemic shock occurring secondary to the ingestion or injection of a foreign substance in which an antigen-antibody reaction cannot be demonstrated. Apparently, these foreign substances may cause the release of chemical mediators in certain individuals.

Etiology

Agents which can precipitate a systemic reaction are so numerous that we have attempted to cover only the most important as well as some of the more controversial or difficult clinical situations as they relate to anaphylaxis. Substances which precipitate the adverse reactions are classified according to the mechanisms outlined by Becker and Austen.[13]

CYTOTROPIC ANAPHYLAXIS

Foods

Although allergic reactions to food are rare, careful investigation of patients exhibiting anaphylactic reactions of uncertain etiology will reveal food factors in an appreciable number. Golbert, Patterson, and Pruzansky detected, within a 1 year period, 15 patients who suffered systemic anaphylactic symptoms after ingestion of an antigen derived from foods.[19] Before their study, a number of investigators had reported anaphylactic reactions following ingestion of either soybean, milk, mango, or orange. Golbert's patients had exhibited potentially fatal reactions with cutaneous, respiratory, and hypotensive manifestations. Eight of them developed recurrent symptoms after inadvertent reingestion of the allergen – and in these the causative agents were pinto bean, halibut, potato, brazil nut, shrimp, and milk. Positive cutaneous reactions to these allergens were observed in 10 of 12 patients tested, and passive transfer to monkey or human skin was accomplished with 8 of 9 sera studied, confirming the role of IgE in the reaction.

Hyposensitization therapy is ineffective and should not be used in managing these patients. Exclusion of the food allergen from the diet is required. This may be very difficult since many food items are improperly labeled as to their content.

Drugs

Certain binding properties of some drugs make them more likely to sensitize. All drugs should be viewed as potential allergens, and none should be prescribed without good reason. This is especially true of those which have already been identified as anaphylaxis inducers, i.e., among others, the following: sodium dehydrocholate (Decholin), thiamine, sulfobromophthalein (BSP), penicillin, demethylchlortetracycline (Declomycin), nitrofurantoin (Furadantin), and streptomycin.[5] Identification by history and careful exclusion are essential, since skin tests and in vitro laboratory procedures are not very helpful. The difficulty of developing proper test antigens for diagnosing drug allergy is illustrated best by the enormous amount of immunochemical investigation with penicillin and its degradation products.[20-25] Specific antigens are available to test for anaphylactic sensitivity to penicillin. However, after 10 years of experimentation, the investigators do not agree as to their findings[25] and the regulating authorities in the United States have not been satisfied that accumulated data presently justify licensing of a conjugated test antigen.

Antisera

Immune sera derived from horses has been given prophylactically against tetanus, diphtheria, rabies, botulism, gas gangrene, and snake bites. Anaphylactic reactions are infrequent. Their incidence in England and Wales following injection of horse tetanus antitoxin has been estimated at 1 per 500,000 injections. Bianchi, in 1967, published an analysis of 146 patients with anaphylactic shock, which developed in 8 after cutaneous testing, in some cases with diluted serum.[26] An immediate wheal and erythema positive skin test is the type of reaction observed in patients with anaphylactic sensitivity. It should be performed before administration of heterologous antitoxin. The antitoxin should be diluted at least 1 to 100, and if the preliminary scratch test is negative, it should be followed by an intradermal test with 0.01 to 0.02 ml. of the diluted antitoxin.[27] Ideal prevention of anaphylaxis is afforded by using human antitetanus or antirabies[28] serum and in such other situations as it may be indicated.

Vaccines

Generalized reactions resulting from active immunization are rare but are quite characteristic when they occur.[29] Hoigne has recently reviewed this subject.[27] Reactions have been reported following immunization with tetanus toxoid, pertussis vaccine, and typhoid vaccine, and this should be kept in mind when vaccinating with these agents. A special note should be made with respect to use of egg embryo grown vaccines. These include measles, rubella, mumps, influenza, yellow fever, and rabies vaccines. A recent encouraging note with respect to these vaccines was presented at the annual meeting of the American Academy of Allergy in 1972 by Miller and Meltzer,[30] who concluded that any patient able to eat eggs at the time of vaccination could be safely vaccinated.[30] The possibility exists that patients who have experienced severe systemic reactions to the ingestion of eggs may also tolerate vaccination with these vaccines. This is indicated by Kamin, Fein, and Britton who reported 11 children to whom egg-derived attenuated measles virus vaccine was administered without consequence in spite of a positive skin test to egg. All 11 children had previously experienced systemic reactions following ingestion of egg, 3 of them having exhibited unusually severe anaphylaxis.[31] Kamin et al. concluded that this vaccine may not contain residual egg allergens.

Stinging Insects

Stinging insects of the order Hymenoptera are important etiologic factors in anaphylaxis. During a 10 year period ending in 1959, 229 persons were killed by Hymenoptera insects.[32] These insects account for more deaths than occur secondary to venomous animal bites.[32, 33] The insects which can precipitate this kind of reaction include wasps, yellow jackets, honeybees, hornets, and ants.[34, 35]

Most commonly, generalized pruritus and urticaria are seen following a sting. Dyspnea, weakness, anxiety, nausea, abdominal cramps, and coma are seen in decreasing frequency.[36] Patients with this group of signs and symptoms should be treated with appropriate Hymenoptera hyposensitization, advised how to avoid being restung, and given emergency kits for self-treatment. Subcutaneous injection of epinephrine remains the most effective means of self-treatment in this emergency situation.[37]

Allergy Extracts

One of the most important areas of concern for allergists and physicians who administer allergy extracts is the likelihood that an anaphylactic reaction will occur. This may occur inadvertently for several reasons including the administration of the wrong dosage, or intravascular injection of extract.[27] Proper technique is paramount in minimizing this risk. The patient should be kept under observation for at least 20 minutes following the injection.[38]

CYTOTOXIC ANAPHYLAXIS

Blood transfusion reactions are the result of red blood cells reacting with antibody with subsequent activation of complement and the release of chemical mediators and hemolysis of cells. The clinical presentation depends on the severity of the reaction. Careful selection of patients for transfusion, proper laboratory techniques, and prompt recognition of a reaction will minimize the risks involved.

AGGREGATE ANAPHYLAXIS

The intravenous and intramuscular administration of human gamma globulin has been shown to produce anaphylaxis.[18, 39–42] The mechanism for this type of reaction remains uncertain, although it may be on the basis of the ability of aggregated gamma globulin to fix complement with subsequent release of histamine.[18] Examples of this form of anaphylaxis are numerous in animal models where the exact in vivo mechanism also remains obscure.[13, 27]

PROTRACTED ANAPHYLAXIS

A human equivalent to this experimental type of anaphylaxis may not exist. However, cases have been reported where following the normal and rapid degradation of medications used in the treatment of anaphylaxis, symptoms have recurred. The mechanism of this type of reaction remains unclear in experimental models. We observed a patient who collapsed following a yellow jacket sting without perception of the sting, respiratory difficulty, or the immediate appearance of a local reaction at the sting site. After resuscitation, a progressively enlarging wheal and erythema over the ankle appeared and persisted for several days. The patient remained hypotensive for 48 hours, requiring intravenous sympathomimetics during this period to maintain normal blood pressure.[43] She subsequently made an uneventful recovery and tolerated hyposensitization with yellow jacket and mixed hymenoptera extract.

ANAPHYLACTOID REACTIONS

Certain substances commonly used in medicine may cause anaphylactoid reactions. In these situations, such as with radiopaque dye reactions, or aspirin-induced asthma, immunologic mechanisms cannot be implicated.[44, 45] The incidence of adverse reactions to iodinated contrast media varies considerably, depending on the procedure or type of examination being performed.[47] Deaths from intravenous pyelograms occur at about 1 per 100,000 examinations, although the number of persons reacting to the dye is much larger. There is no reliable method of predicting who is susceptible to such a reaction. In fact, it is commonly seen in persons receiving the dye for the first time. It has been surmised that these reactions are secondary to the direct action of the injected substances on target cells with subsequent release of chemical mediators. Careful selection of patients for x-ray studies, slower infusion of the media, adequate hydration prior to the procedure, premedication with antihistamines, and use of a test dosage have all been advocated. Two facts are uniformly accepted. First, unnecessary tests should be avoided, and second, the procedure should always be carried out with emergency equipment immediately available.

Ingestion of acetylsalicylic acid can also induce severe life-threatening respiratory distress and subsequent death in a certain group of intrinsic asthmatics.[46] Many of these patients have associated nasal polyps. The etiology of this intolerance is unknown, although it appears to be nonimmunologic.[48] These patients will also many times react to indomethacin, mefenamic acid, and to tartrazine (F.D. and C. Yellow No. 5) in spite of the fact that they have not had previous exposure to these agents. It is interesting that these same patients can ingest sodium salicylate with impunity.[46] Strict avoidance of these agents by these patients is essential.

Local anesthetics are another commonly used agent which is responsible for adverse reactions in patients. True allergic reactions are rare.[49] Although most reactions are attributed to the administration of sympathomimetic agents in conjunction with the anesthetic, or to overdosage because of rapid absorption of an intramuscular injection, there is no satisfactory evidence to substantiate this. In fact, intravenous infusion of xylocaine is frequently used today in the management of cardiac arrhythmias.[50] Although this leaves the vasovagal explanation as the probable cause in many cases, the issue is still a difficult one to deal with clinically.

Patients presumed to be sensitive to local anesthetics should be tested with progressively increasing 10 fold concentrations of anesthetics possessing the p-aminophenyl group and those which lack the p-aminophenyl group (beginning with a 1×10^6 dilution). Representative agents from the p-aminophenyl group include procaine, benzocaine, and pontocaine. The other group includes xylocaine, carbocaine, and nupercaine.[19, 51-53] Those rare persons who clearly develop positive skin tests should be given another type of anesthetic, to which skin tests were negative. Testing will exclude "allergy" but will not prevent non-allergic reactions to local anesthetics.

TREATMENT OF ANAPHYLAXIS

Treatment of any anaphylactic reaction and or laryngeal edema has to be individualized according to the particular etiologic agent involved, the route of administration, and, mainly, according to the clinical signs and symptoms.[54, 55] Tables 1 and 2 outline an approach used by the authors for such a reaction to an injected allergy extract or to an injected medication such as penicillin. This approach, with obvious modifications, is felt to be acceptable for any anaphylactic or anaphylactoid reaction, or for treatment of laryngeal edema. Myocardial infarction must be considered if the patient does not respond to therapy.

PREVENTION

The prevention of allergic emergencies demands that a careful history be taken and the potential hazardous substance for each patient be tabulated and always in view on the patient's record. This suffices for the

Table 1. *Treatment of Anaphylaxis*

1. Place tourniquet above injection site (remove temporarily every 10 to 15 minutes).
2. Place patient in recumbent position and elevate lower extremities.
3. Administer aqueous epinephrine 1:1000, 0.4 cc. subcutaneously or intramuscularly (or if necessary 0.1 cc. in 10 cc. saline solution given intravenously over several minutes) and repeat as necessary.
4. Inject aqueous epinephrine 1:1000, 0.1 to 0.3 cc. at the site of the injection.
5. Establish and maintain airway, first with oral airway. If necessary, use endotracheal tube.
6. Give oxygen at 4 to 6 liters per minute.
7. Monitor vital signs frequently.
8. If patient is not responding, give diphenhydramine hydrochloride (Benadryl), 60 to 80 mg. intravenously over 3 minutes (maximum, 5 mg. per kg. in 24 hours).
9. If blood pressure cannot be obtained, give normal saline intravenously and maintain blood pressure with levarterenol bitartrate (Levophed), 1 or 2 ampules (8 to 16 mg.) in 500 cc. 5 per cent glucose in water, or metaraminol bitartrate (Aramine), 100 to 200 mg. in 500 cc. 5 per cent glucose in water. Titrate to blood pressure.
10. If severe asthma without shock give aminophylline, 500 mg. intravenously over 10 to 20 minutes.
11. While corticosteroids will not be helpful for the acute anaphylaxis, they may prevent protracted anaphylaxis.

Table 2. *Treatment of Laryngeal Edema*

1. Aqueous epinephrine 1:1000, 0.4 cc. every 15 to 20 minutes or as often as necessary.
2. Diphenhydramine hydrochloride (Benadryl), 60 to 80 mg. intramuscularly or intravenously, depending on severity (maximum, 5 mg. per kg. in 24 hours).
3. Maintain airway with oral airway or, if necessary, insert endotracheal tube or perform tracheostomy.
4. Corticosteroids will not be helpful for acute laryngeal edema but will prevent protracted laryngeal edema.

physician treating the patient in his own office or in the hospital. For the patient's protection elsewhere, wearing a Medi-alert tag on which is engraved the substance to be avoided is very useful. The patient must be educated as to the nature of the problem and the specific precautions to be observed. This may mean avoiding a food, wearing a certain color combination when outdoors to decrease the chance of being stung, or carrying a kit containing both injectable and orally active drugs for use when an unavoidable exposure to a hazardous agent has occurred.

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Allergic Lung Diseases Not Mediated by IgE

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The respiratory diseases which result from the interaction of antigen with IgE are discussed in other articles of this symposium on allergic diseases. This section will be concerned with allergic lung diseases associated with other types of immune mechanisms (Table 1), such as immune complex (Type III) reactions, cytotoxic (Type II) reactions, and reactions due to cell-mediated hypersensitivity (Type IV). Each of these immune mechanisms produces characteristic inflammatory changes in the lung, and the immunologic abnormalities involved may often be identified by appropriate testing.[11]

In some of these diseases, a combination of the various types of immune reactions may be involved. The specific immune mechanism(s) involved in pathogenesis is often suspected, but not always ascertained.

CYTOTOXIC (TYPE II) REACTIONS OF THE LUNG

In this type of reaction, circulating antibody interacts with an antigenic component of cells or tissues. The reaction might activate complement and attract polymorphonuclear leukocytes. Reactive enzymes are released[28] and cause damage to cell or tissue.[11] In the kidney, this type of immune reaction can cause a membranous glomerulonephritis; in the blood, hemolysis, leukopenia, or thrombocytopenia. In the pulmonary tissue the cytotoxic reaction may manifest itself as Goodpasture's syndrome. In this lung disease, circulating antibodies are directed against alveolar basement membrane. These antibodies also interact with cross-reacting antigens present in glomerular basement membrane, resulting in damage to the kidney.[28]

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Table 1. *Immune Mechanisms Involved in Allergic Lung Diseases*

TYPES OF MECHANISMS	ANTIBODY	DISEASE
I. Anaphylactic	IgE (IgG)	Asthma associated with Type III
II. Cytotoxic	IgG (Complexes)	Goodpasture's syndrome Other vasculitides
III. Immune-complex	IgG (IgA, IgM, IgE)	Hypersensitivity pneumonitis Serum sickness Periarteritis Systemic lupus erythematosus Other vasculitides Granulomatous diseases, associated with Type I or IV
IV. Cell-mediated hypersensitivity	None (sensitized cells)	Tuberculosis Other fungi Viral diseases? Associated with Type III

The signs and symptoms of the immunologic damage in Goodpasture's disease include hemoptysis, dyspnea, anemia, fever, and pulmonary infiltrations.[18] The nephritis usually becomes evident within a few weeks following the pulmonary manifestations. Death results from progressive renal failure.[18]

Pathologic examination of the lungs reveals varying degrees of alveolar hemorrhage with hemosiderin-laden macrophages within the air spaces. The kidneys demonstrate varying degrees of nephritis with involvement of virtually all glomeruli. The antibody against glomerular basement membrane can frequently be demonstrated by direct or indirect immunofluorescent techniques.[18]

Although the prognosis in Goodpasture's syndrome has been poor, treatment with corticosteroids and immunosuppressive agents has been successful in a few instances.[32] Early bilateral nephrectomy has also been advocated in some refractory and progressive cases in attempts to remove the source of antigen from the circulation.[22]

IMMUNE COMPLEX (TYPE III) REACTIONS OF THE LUNG

In this group of diseases, circulating antigen-antibody complexes formed in the presence of slight antigen excess are deposited or trapped in certain tissues. Complement activation occurs and polymorphonuclear leukocytes are attracted to the site of complex deposition. Cellular lysosomal enzymes are released and cause inflammation of the surrounding tissues.[9, 31] While vasculitis is the usual lesion associated with immune-complex reactions, granuloma formation with giant cell infiltration may also occur.[31]

Hypersensitivity Pneumonitis (Extrinsic Allergic Alveolitis)

Hypersensitivity pneumonitis is one of the possible examples of a Type III reaction. It consists of an interstitial pneumonitis which occurs in sensitized individuals following the repeated inhalation of antigens present in a variety of organic dusts (Table 2). The antigens may be of fungal origin, such as those from thermophilic actinomycetes which grow on vegetable materials (compost, moldy hay, bagasse)[6, 12, 25] or may be found in contaminated air-conditioning or heating systems.[1, 13] Inhalation of antigens derived from animal sources, for instance, of excreted avian proteins,[17, 27] or of parts of insects such as grain weevils,[21] may also cause this disease.

The diagnosis of hypersensitivity pneumonitis is based upon characteristic clinical and serologic features. In the acute form of this disease, sensitized individuals present with recurrent acute episodes of chills, fever, cough, dyspnea, and myalgia, which occur 4 to 6 hours after exposure to the offending agent. Physical examination reveals bilateral basilar end-inspiratory crepitant rales which appear during the acute episode. The attacks may last up to 18 hours with spontaneous recovery but the cough, dyspnea, and rales may persist for several days.[25]

Laboratory abnormalities include a transient leukocytosis, a variable eosinophilia and, in 50 per cent of the cases, a persistent elevation of the immunoglobulin levels. Rheumatoid factor may also be present in some patients. In over 50 per cent of the patients with hypersensitivity pneumonitis, chest x-ray examinations may reveal bilateral diffuse nodular infiltrations. Pulmonary function abnormalities include restriction, a reduced diffusion capacity and, in some cases, a variable degree of

Table 2. *Causes of Hypersensitivity Pneumonitis*

DISEASE	SOURCE	ANTIGEN
I. *Fungal-Associated*		
Farmer's lung	Moldy hay	Micropolyspora faeni
Bagassosis	Moldy sugar cane	Thermoactinomycetes vulgaris
Mushroom worker's lung	Moldy compost	T. sacharii
Contaminated air or heating system	Ventilation system	T. viridis
Malt worker's lung	Moldy malt	Aspergillus clavatus
Sequoiosis	Moldy sawdust	Aureobasidium pullilans
Maple bark stripper's disease	Moldy maple	Cryptostroma corticale
Cheese worker's lung	Cheese mold	Penicillium caseii
II. *Insect-Associated*		
Wheat weevil disease	Contaminated grain	Sitophilus granarius
III. *Serum Protein-Associated*		
Bird handler's lung	Avian proteins	Avian serum proteins and excreta
Pituitary snuff user's lung	Heterologous pituitary powder	Bovine and porcine proteins

obstruction to air flow.[25] Lung biopsies from such patients show lymphocytic infiltrations of the alveolar septa, granuloma formation, and, rarely, vasculitis.[20]

Serologic studies demonstrate precipitating antibodies to the offending antigen in most patients.[25] However, these antibodies may also be found in up to 40 per cent of similarly exposed but asymptomatic individuals.[2] In certain of these entities, for instance in pigeon breeders' disease, skin tests with avian proteins may be of value. An immediate wheal and flare skin reaction, followed in 4 to 6 hours by an Arthus-like inflammatory reaction consisting of erythema and edema, can be demonstrated in most cases. Reproduction of the acute attack may also be accomplished by careful inhalation challenge with the suspected antigen.[25] On the other hand, complete relief of symptoms may usually be achieved by avoidance of exposure.

Manifestations of a more severe and persistent pulmonary impairment may occur in those individuals with more constant and often subtle exposure to the antigenic dust over a prolonged period. Acute attacks are less common in this group of patients. Chronic and irreversible changes may be demonstrated on chest x-ray or pulmonary function testing. Lung biopsy may be necessary in order to establish the diagnosis. Furthermore, corticosteroids may be required for control of the disease since avoidance of the antigen alone may not prove adequate.[25]

The immune mechanism(s) responsible for this group of illnesses has not yet been clearly established. The demonstration of an Arthus-type skin reaction with precipitating antibody is compatible with an immune-complex allergic reaction. However, pulmonary lesions of the Arthus type associated with the deposition of complexes have not been observed in lung biopsies of such patients. In fact, the histologic appearance of the lesions suggests the involvement of cell-mediated immune reactions. Current investigations using animal models have suggested that the pulmonary lesions may be induced as a result of a combination of several immune mechanisms(s), both cellular and humoral.[14]

Asthma Associated with Immune Complexes

Some patients may develop asthma several hours after exposure to a variety of organic dusts such as wood dust,[30] house dust, or mold spores,[4] or after inhalation of certain inorganic materials such as platinum, toluene di-isocyanate or piperazine.[26] The "late" type of asthma in these individuals develops gradually over several hours after exposure, may reach its peak severity over an 8 hour period, and may persist for many hours. It may or may not be preceded by an immediate type of asthma.

The asthma so induced may be quite severe and may be accompanied by leukocytosis with a variable degree of eosinophilia. Furthermore, the bronchial obstruction is relatively resistant to bronchodilators, in contrast to the reversible bronchial obstruction in the more common immediate type of asthma of atopic individuals.[25]

On skin-testing with certain of the suspected antigens, these patients may demonstrate an immediate wheal and flare skin reaction followed by a late-onset skin reaction of the Arthus type. Circulating antibodies of the reaginic and precipitating types have been found in the sera of such individuals. In general, these patients are considered to be non-atopic, since they do not have the broad-based immediate wheal and flare type sensitivities to common inhalant antigens characteristic for extrinsic atopic asthma.[26]

The demonstration of precipitating antibody and the Arthus-type skin reaction, as well as the reproduction of "late" asthma in such individuals, suggests that immune-complexes might be involved. The disease appears to be limited to the bronchial tree and does not affect the peripheral gas-exchanging tissues of the lung as in hypersensitivity pneumonitis.

Dual Type Bronchopulmonary Reactions

In some diseases, such as allergic bronchopulmonary aspergillosis, both IgE (Type I) and precipitating IgG (Type III) immune reactions to Aspergillus species are present. The combination appears to occur most often in extrinsic atopic asthmatic individuals and is associated with severe asthma, migratory pulmonary infiltrations, variable fever, and sputum and blood eosinophilia.[5, 16, 19] The sputum is usually brown and gelatinous and abundant mycelia of Aspergillus fumigatus or other Aspergillus species can be identified microscopically with appropriate staining, or by culture techniques. The characteristic chest x-ray features of this illness consist of shifting peripheral pulmonary infiltrates not limited to one area of the lung. Occlusion of the bronchial tree by plugs of A. fumigatus may result in localized areas of bronchial dilatation. The bronchial tree peripheral to the obstructed area, however, appears normal on bronchographic examination.[25]

Skin tests with extracts of A. fumigatus or other Aspergillus species demonstrate a dual reaction. There is an initial immediate wheal and flare reaction, followed in 4 to 6 hours by an Arthus-type or late reaction.[16, 25]

Both reagins and precipitins to the suspected mold antigens can be demonstrated in the serum of affected individuals and, in contrast to the other forms of allergic lung disease, their levels of IgE are extremely high.[24] Inhalation challenge with an extract of A. fumigatus will reproduce the patient's clinical illness with immediate as well as "late" onset of symptoms. The dual reaction is probably the result of the interaction of A. fumigatus antigen with both IgE and IgG antibodies. Such interaction has been demonstrated by the passive transfer of serum from patients with allergic bronchopulmonary aspergillosis to monkeys and production of the characteristic pulmonary and skin lesions.[15]

Corticosteroids are indicated in the management of allergic bronchopulmonary aspergillosis. Therapy with specific antifungal agents or hyposensitization has not been rewarding.

Other Types of Immune Complex Lung Disease

Pulmonary manifestations may be associated with a wide variety of systemic diseases known or suspected to be the result of the deposition of toxic-immune complexes and the involvement of complement and leukocytes. Such diseases include the collagen group (systemic lupus erythematosus, rheumatoid arthritis, and scleroderma), pulmonary vasculitis, and serum sickness, as well as certain drug reactions.

These diseases are frequently associated with diffuse and progressive interstitial infiltration with pulmonary vasculitis, hemorrhage, necrosis, granuloma formation, and at times fibrosis.[7, 8, 23, 33] The clinical features include progressive dyspnea, usually with the absence of wheezing, and a restrictive ventilatory impairment with reduction of the diffusing capacity. Therapy is directed against the primary disease and often requires corticosteroids as well as immunosuppressants.

Immunologic studies of this group of diseases have demonstrated the presence of a variety of nonspecific auto-antibodies such as antinuclear antibody, rheumatoid factor, anti-RNA or anti-DNA antibody, and so forth.[10, 29] The role of these antibodies in the pathogenesis of the lung disease is unclear.

CELL-MEDIATED (TYPE IV) REACTIONS OF THE LUNG

Cell-mediated (Type IV) reactions cause tissue damage in such diseases as tuberculosis and fungal infections. Cell-mediated allergy cannot be ruled out in hypersensitivity pneumonitis, in pulmonary diseases presumed to be due to immune complexes, or even in some forms of "common" bronchial asthma. Further investigations will be necessary to evaluate the possible, primary or secondary, role of cell-mediated immunological responses in the genesis of allergic lung disease.

SUMMARY

It is apparent that the lung may be the target organ for all four types of allergic reactions. The manifestations of the resulting pulmonary disease are probably dependent upon the genetic characteristics of the individual, the nature and duration of exposure to the antigen, the type of immune response, and the site within the lung at which the reaction occurs. Furthermore, one or more types of allergic reactions may probably interact in the lung, resulting in the production of specific disease. Although the immunopathogenesis of certain of the allergic pulmonary diseases, in particular of IgE-mediated asthma, is relatively well understood, the factors which encourage the development of the other allergic pulmonary diseases remain to be elucidated.

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The Adult Skin and its Potential for Allergic Reactions

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The skin has the ability to develop allergic reactions and does so with disconcerting frequency. Beyond that fact, the mechanisms which underlie the cutaneous allergic response, the exact nature of the causative antigen, the discrimination of the antibodies produced, the nature and sequence of the mediators of inflammation, and the characteristics of the repair cycle remain, in large part, a mystery. Data continue to be gathered, and more appears to be known about contact dermatitis and anaphylaxis than about cell-mediated immunity, but, as Stewart[1] has recently stated, "increasing scientific effort leads us from the comparative bliss of ignorance to the confusion of knowledge."

Changes in perspective, however, are certainly taking place. Diseases previously considered "allergic" in nature by most authors are now thought by many probably not to be mediated by antigen-antibody mechanisms. Some examples are fixed drug eruption, some cases of Lyell's syndrome, Stevens-Johnson syndrome, erythema nodosum, and atopic dermatitis. Other diseases of the skin, such as pemphigus vulgaris and bullous pemphigoid, increasingly are being considered expressions of autoimmunity, whereas previously their causes were totally unknown.

It will be the purpose of this article to examine current opinion concerning the relation of a number of cutaneous abnormalities to allergy. We will also examine the effectiveness and usefulness of a number of diagnostic procedures carried out on the skin itself. We will not discuss urticaria, perhaps the most common cutaneous expression of allergy, since emphasis is given to that topic elsewhere in the volume.

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CONTACT DERMATITIS

Allergic contact dermatitis must be distinguished from primary irritant contact dermatitis. This distinction, easily made in texts, may be quite difficult to make in a clinical setting, and it is here that the appropriate use of the patch test may be helpful. But finding the presence of an allergen does not necessarily exclude a host of other factors which must be considered and dealt with in the management of the patient, such as primary irritants, rubbing, excessive hand washing, and overtreatment.[2]

Allergic contact dermatitis results from the binding of relatively simple chemical group(s) to an epidermal protein to form a complete antigen. The reaction has a delayed onset and causes tissue damage, presumably mediated by a mechanism similar or identical to Type IV allergy.[3] At the same time, an immediate humoral or Type 1 allergic reaction may be stimulated.[4]

The inflammatory reaction in contact dermatitis is characterized by a mononuclear cell infiltrate. The result of the allergic sensitization is an eczematous reaction consisting of redness, intra-epidermal edema (spongiosis), weeping, scaling, and thickening of the skin. When the eczematous reaction is highly localized to an obvious area of contact (i.e., the wrist, from a watch band; the ear lobe, because of earrings; etc.), the diagnosis is simple and treatment usually efficacious and expeditious. However, unlike the period in history when the allergenic hazards in the environment were limited to the plant kingdom, our society today permits exposure to numerous synthetically produced chemicals hidden in environmental contactants or airborne so that the allergen may not be obvious from the distribution pattern of the eruption. A careful appreciation of the morphological characteristics of an eczematous eruption, the exhaustive search for pertinent historical data, the dogged and appropriate use of patch testing, and the presence of constant suspicion are the most helpful and powerful tools in diagnosing the nature of an allergic contact dermatitis.

Baer, Ramsey, and Biondi[4a] studied 200 patients for allergic contact dermatitis to 24 common antigens by patch test. Positive patch tests to each of them were found in 3 per cent or more of the patients (3.1 to 22.2 per cent). The ten most sensitizing of these allergens (7.9 to 22.2 per cent reacting) were mercury bichloride, mercaptobenzothiazole, paraphenylene diamine, potassium dichromate, ethylenediamine, nickel sulfate, turpentine oil, formaldehyde solution, poison ivy, and bismarck brown.

At least three major problems in the area of allergic contact dermatitis remain to be resolved. First, it would be most desirable to have an in vitro method of determining the causative agent, since at present we must resort to the production of the disease in miniature (a patch test) in order to ascertain the cause. Second, we should have the ability to predict effectively which agents are most likely to sensitize. Finally, if a dermatitis develops it would be helpful to have greater knowledge about the chemical mediators of the acute inflammatory response which follows the sensitization, so that more effective therapy could be employed to combat the early stages of the process. In each of these areas a considerable number of studies have moved us toward a solution, but at this time the answers are still not at hand.

In vitro techniques leading to a definitive diagnosis have centered around two major procedures: the lymphocyte transformation test and the migration inhibition test.

Milner,[5] Hutchinson,[6] and Milliken,[7] among others, have found the lymphocyte transformation test useful in identifying haptenes which have caused contact dermatitis. The procedure requires that lymphocytes be cultured in the presence of a conjugate of a haptene and skin protein from a sensitive donor. An increase in radioactive thymidine incorporation is detectable with sensitized, transforming lymphocytes. These findings have not been consistently confirmed,[8] but differences in techniques may account for the early variability in the reproducibility of this test.

Macrophage inhibition factor is a low molecular weight substance produced by T-lymphocytes[9, 10] stimulated by the appropriate antigen and inhibits normal macrophage migration. Nishioka and Amos[10] studied the efficacy of subcellular fragments of DNCB-painted epidermis in producing macrophage inhibition factor from lymphocytes of lymph nodes from DNCB-sensitized guinea pigs. These authors found that some subcellular microsomes contained a protein component which, together with the appropriate haptene, did stimulate production of macrophage inhibition factor under their laboratory conditions.

A simple test in laboratory animals which would effectively predict the probability of a topically applied chemical becoming a significant sensitizer would be a boon to physicians, patients. the pharmaceutical industry, the Food and Drug Administration, and the cosmetic industry. A great deal of work has been done in this area by Hunziker,[11] and Magnusson and Kligman,[4] among others, since the early studies of Landsteiner and Draize. Magnusson and Kligman maximized (i.e., magnified the factors involved in sensitization) the patch test in guinea pigs by using younger animals, giving the antigen mixed with adjuvant by injection, followed by topical application, using the most effective skin site, increasing the concentration of antigen, applying the substance more frequently, using a greater volume, adding irritants to the antigenic stimulus, etc. The greater sensitizing potential of this animal model seems well documented and correlates well with Kligman's maximization procedures in the human being. The efficacy of these procedures as predictors await the results of longitudinal prospective studies.

The acute inflammatory response which clinically signals the presence of Type IV allergy is initiated by a host of short-acting chemical mediators, including histamine and acetylcholine. The later stages of acute inflammation which progress to subacute inflammation are probably stoked by an additional cascade of chemical events, some of which are now being defined. Rajkumar and Solomon[12] have recently reviewed the role of prostaglandins in cutaneous biology, including their role in cutaneous inflammation. Prostaglandin E_1 is capable of causing long-lasting (up to 10 hours) inflammation and pain,[13] and it is of interest that Greaves and Sondergaard,[14, 15] using skin perfusion techniques, have recovered prostaglandins from the skin of a majority of subjects studied with allergic contact dermatitis. The fact that acetylsalicylic acid is a blocker of prostaglandin synthesis may explain the beneficial effects of aspirin on inflammation.[16] Prostaglandin may also interact with complement in the inflammatory response. The action of cyclic AMP in release of histamine and slow-reacting substance A (SRS-A) in IgE-mediated responses has been studied[17, 18] and shown to be operative, but the role of cyclic AMP and the phosphorylating enzymes such as the protein kinases in allergic contact dermatitis remains to be elucidated.

Although the light microscopic features of primary irritant dermatitis are essentially indistinguishable from those of allergic contact dermatitis, recent evidence[19] suggests that electron microscopic changes may be used to discriminate between the two processes. The changes in primary irritant dermatitis were found to be related to damage of the dermoepidermal junction and necrosis of epidermal cells. In allergic dermatitis, spongiosis and the presence of secondary lysosomes were the primary features, but these features were lacking in the primary irritant process.

In the absence of a satisfactory means of prevention, the sine qua non for effective treatment of allergic contact dermatitis is removal of the offending agent. Symptomatic relief of the dermatitis can be achieved by the application of cool water compresses to the acute weeping phase, calamine lotion to the subacute phase, and topically applied corticosteroid creams and ointments to speed the resolution.

THE PATCH TEST

The patch test has remained a useful instrument for studying contact sensitizers and photosensitizers (see below). The technique for performing patch tests is essentially the same as that used by Jadassohn and by Jean Henri Fabre (the entymologist) in 1895, when he tried to discover the cause of blistering produced by caterpillars.[20]

The suspect material (clothing, household chemical, food, cosmetics, etc.) is applied to an area of normal skin for 48 to 72 hours and held in place by adhesive tape. The tape is then removed, and the exposed skin is examined for a vesicular or eczematous reaction (redness, "bubbly" surface, weeping).

Some fine points about the technique are as follows: Test only an area of normal healthy skin; if the material you wish to use is liquid, place a few drops on a 1 cm. square piece of white filter paper, cotton, or linen; isolate the suspect substance from the adhesive by placing a 1½ cm. square piece of polyethylene film over the filter paper, and then place the adhesive over the impermeable film, occluding its borders (this is done in order to separate reaction to the sensitizer from reaction to the adhesive); use concentrations of the suspected sensitizer which do not irritate the skin;[*] it is best to postpone all patch testing until the presenting eruption has substantially subsided; mucus membranes are generally poor areas for patch testing since reactions can rarely be elicited.

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[*] Most useful treatises on patch test concentrations and contact dermatitis may be found in Fisher's text[21] and in the article by Baer and Witten.[22]

Some special precautions deserve to be mentioned when considering the procedure of patch testing. There has been debate in recent years about whether or not the positive results of patch tests could be suppressed by oral corticosteroids. It has recently been demonstrated[23b] that 40 mg. of prednisone ingested daily for 7 days did decrease, but did not suppress entirely, the patch test reaction in subjects sensitive to poison ivy. Since mild positive reactions are difficult to interpret anyway, it may be wise not to attempt patch testing in those patients who are receiving corticosteroids. A second source of error may be found in attempting patch tests on eczematous skin in patients with widespread atopic dermatitis where occlusion alone may promote itching, scratching, and, therefore, false-positive reactions.

Special Patch Tests. The *photopatch test* is discussed below. In the *open patch test* the occlusive dressing is simply omitted. The suspect substance is placed on the skin and allowed to dry, and the site is examined 48 hours later.

The *provocative patch test* requires alteration of the permeability of the test site stratum corneum by sodium lauryl sulfate prior to application of the patch. This procedure requires practice and training in interpreting the results.

Special Uses of Patch Tests: Apart from the general usefulness of patch tests in identifying suspect sensitizers, they may be used as well for predictive purposes (see section on contact dermatitis above) and to evaluate the adequacy of cell-mediated immunity in patients with suspected immunodeficiency. In the last procedure the patch test is used to elicit the response in a subject who is deliberately sensitized to dinitrofluorobenzene (DNFB) or dinitrochlorobenzene (DNCB).

DRUG REACTIONS

The term cutaneous drug reaction refers to the unwanted effects of a systemically administered drug on the skin. Urticarial reactions will be discussed elsewhere in this volume and are omitted to reduce replication. Photoallergy will receive separate attention. For a review of the nonallergic aspects of drug reactions the reader is referred to a recent review by Schuppli.[23]

The clinical spectrum of cutaneous reactions to drugs may conveniently be discussed according to a number of morphologically distinct types. The benefits of such a classification are twofold. First, it is the cutaneous expression of the reaction (i.e., the rash) with which the physician is confronted in his office. Therefore, a morphologic classification deals with the problem rather than the solution (a classification of cutaneous allergy based on histopathologic features or one related to the causative drugs would be one based on the solution). Secondly, a morphologic classification of drug reactions permits rapid differentiation of those reactions which are potentially life-threatening from those of a more benign nature. In addition, a morphologic classification of drug reactions in no way inhibits the subsequent reclassification of drug reactions for more basic pathophysiologic reasons.

The cutaneous reaction patterns which drugs may elicit are as follows:

1. Bullous eruptions, including erythema multiforme and Lyell's syndrome.
2. Exanthematous eruptions usually referred to as "nondescript" but consisting of macules or maculopapular lesions.
3. Eczematous eruptions which often start as maculopapular eruptions but progress to weeping, scaling, and sometimes exfoliation.
4. Urticaria.
5. Purpuric eruptions which may reflect intravascular coagulopathy or vascular damage.
6. Nodular eruptions which may result from diverse reactions (such as erythema nodosum, vasculitis, panniculitis, or granuloma formation).
7. Fixed drug eruptions whose allergic origin is doubtful.[23a]
8. Photoallergy requiring the interaction of a drug and light.

A single drug may cause diverse reactions in different individuals, diverse reactions in the same subject at different times, or diverse reactions at the same time on different surfaces of the body (i.e., erythema multiforme). Furthermore, many drugs may produce identical reactions. The more serious and potentially life-threatening reactions are probably the bullous eruptions (Rostenberg and Fagelson), exfoliative eruptions, and urticaria (when laryngeal edema ensues).

Turk[24] believes that "the molecular size of the complex formed is probably critical in determining the form of the lesion seen in the skin in all these reactions, as this will determine the size of the blood vessel and thus the level in the dermis at which the reaction occurs." This may be true in those drug reactions where an antigen-antibody reaction is directly responsible for the lesion. However, the vast majority of drug eruptions act in a most unpredictable manner, and the nature of the reaction may depend as much on the peculiar genetic make-up of the host and local deficiencies in the target organ as on the size of the immune complexes formed – if indeed immune complexes are responsible for many drug eruptions.

Bullous Eruptions

Bullous eruptions may have many causes (see pemphigus, p. 175), and those eruptions caused by drugs must be differentiated from those of other causes. Drug-induced bullous eruptions are of three major types: erythema multiforme, which, when it involves mucous membranes and has serious systemic manifestations, is called Stevens-Johnson syndrome; Lyell's syndrome (toxic epidermal necrolysis, scalded skin syndrome), and bullous fixed drug eruption. The last is quite rare. Although the location of the blister in the skin (subepidermal in erythema multiforme and usually intra-epidermal in Lyell's syndrome) may help to differentiate Lyell's syndrome from erythema multiforme, there is frequently difficulty in distinguishing the two conditions. Bullous eruptions may have causes other than drugs, including infection with Staphylococcus aureus of group II phage types (especially in Lyell's syndrome in infants), viruses, and malignant tumors. The lines separating erythema multiforme and Lyell's syndrome of drug versus infectious origin are not always clear, especially since the eruption often follows the administration of a drug for a systemic disease. It therefore becomes difficult to searate the drug as cause from the underlying process as trigger. Kauppinen[25] recently reviewed the literature on bullous drug eruptions. He also studied 60 patients with possible drug-induced bullous eruptions and found 36 had Lyell's syndrome, 16 Stevens-Johnson's syndrome, and eight bullous fixed eruptions. In only one case of Lyell's syndrome did a provocative test confirm the likely probability that a drug, carbamazepine, caused the eruption. Seventy-eight per cent of the remaining 35 patients with Lyell's syndrome had ingested sulfonamides, either alone or in combination with other drugs. Three of the 36 patients died as a result of their eruption, and all 3 had received sulfamethiazole and sulfamethoxypyridazine for a urinary tract infection. There were no fatalities among 8 patients with bullous fixed drug eruption, and in all 8 patients provocation tests were positive. The drugs incriminated were phenobarbital, phenazones, and sulfamethoxydiazine. The findings of Kauppinen support those of Rostenberg and Fagelson,[26] among others, that long-acting sulfonamides have been among the most frequent causes of fatal bullous reactions.

It should be noted that a positive provocation test may prove a drug as the cause of an eruption, but it does not confirm an allergic mechanism. One would, for example, find a very high yield of positive provocation tests to primaquin in patients with 6-glucose phosphate dehydrogenase deficiency, yet the cause of the sensitivity to the drug is an enzyme deficiency rather than allergy.

Exanthematous Eruptions

The mild, self-limited, macular or maculopapular eruption which disseminates rapidly and is pruritic is a common occurrence. It may be viral in etiology or, in the absence of systemic manifestations, may be ascribed to a drug. A typical example of this kind of eruption is that seen in the vast majority (80 per cent or more) of patients with infectious mononucleosis who have received ampicillin. The striking incidence of ampicillin eruptions in patients with infectious mononucleosis is at present unexplained and must be contrasted to the lesser incidence (less than 1 in 10 patients) of ampicillin eruptions in the general patient population. There is apparently no relationship between the incidence of eruptions and the brand of ampicillin used.[27] In Kauppinen's study[25] the drugs which most frequently caused exanthematous eruptions among 638 affected individuals were chloramphenicol, sulfonamides, barbiturates, penicillin, ampicillin, tuberculostatics, nitrofuran derivatives, and aspirin.

Nodular Eruptions

Nodular drug eruptions are very rare. In one study of 343 patients with erythema nodosum only 6 cases were ascribed to a drug, 4 to penicillin, 1 to phenacetin, and 1 to pyrithioxin.[28]

Eczematous and Exfoliative Drug Eruptions

Exfoliative drug eruptions are seen less frequently than in the past, probably because of a decrease in the use of arsenicals. Nevertheless they sill occur occasionally, and the most frequently incriminated drugs are diphenylhydantoin (possibly as part of the pseudolymphoma syndrome), sulfonamides, thiazides, phenylbutazone, and gold.

We could not in this concentrated review attempt to cover the voluminous literature on reported reactions to specific drugs. The reader may delve into this aspect of the subject by consulting the Medical Letter, Clin-Alert, and the more than twenty quarterly reviews in the British Journal of Dermatology.

PHOTOALLERGY

Epstein[29] recently defined photoallergy as "an acquired altered capacity of the skin to react to light energy alone or in the presence of a photosensitizer, which is presumably dependent on the development of a circulating antibody or a cell-mediated immune response." This definition distinguishes the photoallergic phenomenon from the phototoxic reaction. Both photoallergy and phototoxicity (together they are part of a larger category of skin abnormalities generally referred to as photosensitivity reactions) may be caused by drugs. We will concern ourselves here primarily with photoallergy. However, by way of contrast, it should be noted that phototoxic reactions may occur in every individual exposed to the chemical involved, be it administered systemically or topically. The phototoxic reaction is like a primary irritant reaction and results from a lowered cutaneous threshold to damage by light. The clinical expression of a phototoxic reaction is usually similar to an acute sunburn reaction (redness and swelling) and occurs a few minutes after an unusually small exposure to sunlight. All subjects taking a phototoxic agent have a lowered erythema threshold (also called minimal erythema dose or MED) to ultraviolet light. The essential immunologic characteristics which differentiate phototoxic from photoallergic reactions may be found in a recent review by Harber and Baer.[30]

Photoallergic reactions may occur as a result of administration of a drug systemically or topically and probably requires the alteration of an intracellular or extracellular protein by light, which induces a change in the protein's epitopes, making it antigenic. The presumed sequence of events[30] that culminates in cellular damage in drug-induced photoallergy is as follows: The photosensitizing substance exposed to light absorbs energy, and the resultant molecule enters a state of excitation. Excitation may result in fluorescence and phosphorescence. Free radical formation and/or oxidation of the excited molecule leads to a new haptene formation. The haptene combines with protein, becoming a complete photoantigen. From this point forward the events resemble those of any cell-mediated allergic reaction.[31]

The wavelengths of the photons absorbed by the chemical substance is called the *absorption spectrum* and is measured in vitro by spectrophotometry. The *action spectrum* refers to the wavelengths which cause a clinical disorder in the skin and is determined by exposing the skin to a series of wavelengths (the light source is preferably monochromatic).

The clinical expression of photoallergy is similar whether the drug is applied to the skin or ingested. In the former instance the eruption is limited to those areas of the skin on which the drug has been applied and which have been exposed to light. If the photoallergen has been systemically administered all areas exposed to light may be affected. The production of such an eruption requires repeated exposure to the drug, an incubation period for development of the photoantigen, and a variable latent period of hours between the development of the eruption and exposure to light. Photoallergic eruptions are usually papular, lichenoid, or eczematous, and histological sections of these lesions often show a spongiotic eczematous picture.

The diagnosis of a photoallergic eruption demands above all a high index of suspicion. An eczematous eruption in light-exposed areas or with an onset related to light exposure requires a careful history, particularly with regard to known photoallergens. Topical contact photosensitizers include some aftershave lotions, psoralens, brighteners in detergents, sulfonyl carbamides, the halogenated salicylanilides, phenothiazines, and even sunscreens.[29] The more important systemic photosensitizers include phenothiazines, thiazide diuretics, sulfonamides (including the closely related sulfonylureal hypoglycemic agents), oral contraceptive hormones, calcium cyclamate, and chlordiazepoxide hydrochloride.[29]

The diagnostic confirmation of contact photosensitizers can be made by photopatch testing. The difference between an ordinary patch test and a photopatch test is that in the latter procedure two patch tests must be applied and covered with black paper for one or two days. Then one patch is uncovered and irradiated with an appropriate light source, such as a carbon or xenon arc lamp, or sunlight filtered through window glass. Twenty-four hours later the patches are examined and read as a regular patch test. The unirradiated control patch signifies the contact sensitizing properties of the suspect material as opposed to its photosensitizing properties.[32]

The diagnosis of a reaction to a systemically administered photosensitizer is made much like any drug eruption – on historical grounds and on the appearance of the eruption. Supporting evidence (though not diagnostic) can be gathered from histologic examination of a biopsy specimen.[29]

Treatment of a photoallergic reaction requires: (a) removal of the offending agent, (b) avoidance of light and the use of a sunscreen applied to the skin, and (c) treatment of the acute inflammatory response with topical steroid creams. The prognosis of most patients with a photoallergic eruption is usually good, but some patients remain sensitive to light for years, even though the offending cause has been removed.[30]

ATOPIC DERMATITIS

For many years few treatises on allergy neglected to include atopic dermatitis, a disease considered allergic in origin by most authors. The frequent presence of eczema in families with other atopic diseases such as hay fever and bronchial asthma and the presence of circulating antibodies, then called reagin, now identified as IgE, seemed to support that conclusion. There are, however, discrepancies in the allergic theory of atopic dermatitis. Evidence has recently been accumulating which points to the conclusion that not only is atopic dermatitis not a disease of allergy, but that it possibly represents, among other things, a state of cellular immunodeficiency.[33, 34] Although serum IgE levels were found to be higher in patients with atopic dermatitis than in those with other dermatoses,[35, 36] extremely high levels are found in patients without atopic dermatitis,[37] and atopic dermatitis is found in patients with low serum levels or no IgE at all.[38]

Patients with atopic dermatitis have a lower clinical incidence of allergic contact dermatitis than patients with stasis dermatitis, and no greater incidence than patients with other dermatoses.[39, 40] Jones, Lewis, and McMarlin[33] have demonstrated that the incidence of allergy to poison iy is ten times *less* frequent in patients with atopic dermatitis than in the general population and have hypothesized that atopic dermatitis may "be a phenotypic marker for a defect in the human cell-mediated immune system." Support for this thesis was previously published by Lobitz, Honeyman, and Winkler.[34]

These and other findings recently reviewed by one of us[41] lead to the conclusion that, contrary to past opinion, atopic dermatitis is not allergic in origin but is probably a hereditarily determined lowered cutaneous threshold to pruritus and possibly related to a metabolic defect in the skin.

AUTOIMMUNITY AND CUTANEOUS DISEASE

The concept of autoimmunity has been the stimulus for impressive advances in our understanding of pathogenetic mechanisms involved in both multisystem and organ-specific diseases. In the autoimmune disorders, tissue damage is believed to occur as a consequence of an immunologic reaction of the host with his own tissues, but the exact relationship of the autoimmune phenomenon to the disease process itself is as yet largely unknown. Until recently the suggestion that autoantigens might be implicated in certain skin diseases had been merely speculative; however, the findings accrued from the application of immunofluorescent techniques have provided more convincing evidence for immunologic reactions involving cutaneous structures. Within recent years antibodies to components of epithelial tissue have been detected in a number of cutaneous diseases—most notably lupus erythematosus, bullous pemphigoid, and pemphigus. Less certain is the participation of such antibodies in other disorders, such as dermatitis herpetiformis, the gyrate erythemas, and hypersensitivity angiitis.

For the clinician, positive immunofluorescent studies can provide valuable ancillary information, particularly when he is faced with an equivocal diagnostic situation. Basically, two procedures have been utilized to establish the presence of antibodies to autologous skin. To detect in vivo bound antibody, the direct immunofluorescent technique is employed. This requires a fresh skin biopsy which has been snap-frozen in liquid nitrogen or solid carbon dioxide and must remain frozen until cryostat-cut sections are obtained. These sections are then incubated with fluorescein-conjugated whole anti-human globulin or with fluorescein-conjugated IgG, IgM, IgA, IgD, IgE, and B_1C. When the tissue is examined under a fluorescence microscope the presence of bound antibody is identified by specific staining patterns.

The indirect technique is used to demonstrate circulating antibodies to cutaneous structures. In this method the serum is layered onto sections of normal epithelial tissue [which may be obtained from humans, primates, guinea pigs (lips or esophagus), or rabbits (esophagus)]; during the initial incubation period the patient's antibody is fixed to the epithelial substrate. Fluorescein-conjugated whole or fractionated anti-human globulin is then applied to the serum-treated sections and will tag any tissue-fixed antibody which may be present. The slides are examined with a fluorescence microscope as in the direct technique.

These relatively simple laboratory procedures using readily available material (skin and serum) are not without pitfalls. Nevertheless, in experienced hands, the data from immunofluorescent tests can be used not only to support a clinical impression, but also offer a means by which the therapeutic response of the patient can be evaluated.

Pemphigus

Pemphigus vulgaris[42] is a relentlessly progressive, chronic bullous disorder which was usually fatal prior to the advent of corticosteroids and immunosuppressive agents. Although in some patients the early course may be indolent, with lesions restricted to localized areas, in others the onset is explosive with rapid dissemination of bullae over widespread areas. The bullae arise from either a noninflammatory or erythematous base, become flaccid as they increase in size, and rupture easily because they are relatively superficial, leaving a denuded area with detached epidermis at the periphery. In the active phase of the disease simply the pressure of the examiner's finger may dislodge the epidermis from apparently uninvolved areas of skin (Nikolsky's sign). Healing is poor, and erosions may enlarge and become secondarily infected. Mucosal lesions occur with high frequency in pemphigus and may be the presenting sign of the disease. Oral involvement is often severe, causing extreme debility and intense pain. The patient with pemphigus frequently appears ill and shows signs of toxicity, although why this occurs is not clear.

Histologically, pemphigus is separable from other bullous disorders on the basis of the light microscopic findings. Early bullae show clefting and separation immediately above the basal epidermal cells. Clustered and solitary epidermal "acantholytic" cells, many of which are degenerated and altered in appearance, float free in the blister cavity. Once the blister ages, these changes may become obscured by the process of regeneration. Cytologic examination of smears obtained from the base of an intact blister (Tzanck smears) will also demonstrate the characteristic acantholytic cells. Ultrastructural studies have suggested that retraction of the prickle cells' tonofilaments and dissolution of the desmosomal attachment plates may account for the phenomenon of acantholysis. Curiously, the half-desmosomes which hold the basal cells in contact with the basement membrane seem to remain intact. However, a more recently held view is that the initial site of damage is actually the epidermal intercellular cementing substance and that the changes in the tonofilaments and desmosomes represent a secondary event.[43] The importance of the sequence of events in the evolution of the pemphigus blister has subsequently derived further support from the studies of Chorzelski et al.,[44] who confirmed that, at the ultrastructural level, pemphigus antibody was localized to the intercellular space.

Although for many years some attributed pemphigus to viral infection or metabolic derangement, no firm data were forthcoming to support either of these supposed etiologic mechanisms. In 1964 Beutner and Jordan[45] demonstrated the presence of skin autoantibodies in the serum of patients with pemphigus vulgaris, thus implicating immunologic factors. The antibody binds to the surface of the stratum spinosum cells (prickle cells), outlining the boundaries of these cells, and is thought to be directed against the intercellular cementing substance localized at these sites.[44, 46] Extensive studies from several laboratories have confirmed the finding that fresh lesions from patients with pemphigus show characteristic intercellular staining with the direct immunofluorescent method. The normal skin contiguous to the bullae is also strongly reactive, but fluorescent staining of distal uninvolved skin gives inconstant results.[47] Skin lesions with a histologic picture atypical for pemphigus vulgaris may show the characteristic immunofluorescent pattern, but tissue from mucosal lesions can give misleading results and should not be relied upon for diagnostic purposes.[48] Circulating antiepithelial antibody is present in patients with active disease and can be titered by the indirect technique; in general, the height of the antibody titer is proportional to the severity of the disease.[49] Both circulating and bound pemphigus antibody have been identified as IgG.[47] Whether or not complement is involved in the pathogenesis of the disease or is, in fact, consistently present in the pemphigus lesions has remained a matter of dispute.[50, 51]

Attempts to elicit the autoantibodies and pemphigus-like skin lesions in animal models have met with varying degrees of success. Grob and Inderbitzin[52 53] were able to stimulate high titers of circulating antiepithelial antibodies in rabbits but could not elicit acantholytic lesions without pretreatment of the skin with sodium lauryl sulfate and dry ice. The inoculation of primates with serum of high antibody titer from patients with pemphigus resulted in the fixation of the pemphigus antibody to the epidermal intercellular spaces as in human skin, but clinical lesions failed to develop.[54] However, subsequent attempts using other animal models are said to have yielded more fruitful results.[48]

The origin and role of the pemphigus antibody is still under debate. The localization of antibody to the disease site, its specificity, the correlation of antibody titer with severity of disease, and the partial success of studies in animal models lend credence to the view that autoantibodies are essential to the disease process. Nevertheless, a definitive role in the pathogenesis has yet to be established.

Dermatitis Herpetiformis

As a result of the negative findings in early immunofluorescent studies, dermatitis herpetiformis was initially excluded from the group of cutaneous disorders attributed to or associated with autoimmune phenomena. This distinction also seemed valid on clinical grounds, since the lesions of dermatitis herpetiformis are most often papulovesicular (rather than bullous), are extremely pruritic, and resolve when treated with sulfones or sulfapyridine, in contrast to pemphigus and bullous pemphigoid, which respond to immunosuppressive agents. However, in subsequent studies utilizing the direct immunofluorescent technique, granular deposits of globulins (mainly IgA and complement) could be identified at the junction of dermis and epidermis, particularly in the tips of dermal papillae of the uninvolved skin.[55] Accumulated data from larger numbers of patients with dermatitis herpetiformis have underscored the tremendous variability of these immunofluorescent patterns.[56, 57] The deposits of immunoglobulin, when present, appear granular, fibrillar, globular, or, less commonly, homogeneous. IgA invariably predominates, but IgG and IgM are also occasionally detectable.

The congruity of intestinal malabsorption and abnormalities of the jejunal mucosa with the cutaneous eruption of dermatitis herpetiformis has generated widespread interest in this disorder. Nevertheless, clarification of the association between the cutaneous lesions and the bowel disorder has proceeded slowly. The enteropathy of dermatitis herpetiformis resembles adult celiac disease in that it is gluten-sensitive and improves after gluten withdrawal, whereas the relationship between gluten-sensitivity and the skin lesions of dermatitis herpetiformis is less clear.

Dick et al.[58] reported the occurrence of both fixed and circulating antibodies to the basement membrane zone of the jejunal mucosa in patients with dermatitis herpetiformis, but Holubar and his colleagues[56] were unable to confirm these findings. Immunologic mechanisms have been further implicated by the discovery that patients with dermatitis herpetiformis have other types of autoantibodies. Circulating antinuclear factor,[59] thyroid microsomal and gastric parietal cell antibodies,[59, 60] thyroglobulin antibody,[60] and antibody against connective tissue[59] are found in a significant number of patients with dermatitis herpetiformis. The connective tissue antibodies are thought to be directed against reticulin[59, 61] rather than collagen, since pretreatment of tissue sections with collagenase does not impair the immunofluorescent reaction, and the pattern closely resembles that obtained with silver-impregnation staining for reticulin. In addition, immune complexes, probably of IgG class, have been detected in the serum of patients with dermatitis herpetiformis by an anticomplementary method.[62]

The enteropathies of dermatitis herpetiformis and adult celiac disease appear to be similar in many respects; however, skin lesions occur only in the former disease. One fascinating hypothesis[62] suggests that both diseases require the presence of circulating antibodies to the bowel reticulin, but that in dermatitis herpetiformis the defect is more widespread, involving dermal reticulin as well. Since it has been demonstrated that dietary gluten and reticulin have some cross-reactivity,[61] damage to the connective tissue by gluten might permit the formation of immune complexes which then become trapped in the dermis and result in clinical lesions. The fixation of complement by these complexes might explain some of the histologic features (e.g., the polymorphonuclear leukocyte response) of the subepidermal dermatitis herpetiformis blister.

Bullous Pemphigoid

In 1953 Lever[63] first defined this disorder as a separate clinical entity, but in 1967 immunologic studies[64] provided convincing evidence for the consideration of bullous pemphigoid as a specific disease. Although the characteristic basement membrane zone antibody has become one of the diagnostic criteria for the disease, the experienced clinician can often identify these patients with reasonable certainty on the basis of the physical findings alone.[42]

Bullous pemphigoid is seen predominantly in adults, with a predilection for the elderly. The typical blister is tense, large, irregular in outline and occasionally hemorrhagic, but may become flaccid after partial resorption or drainage of fluid. Once the bullae have ruptured, the resultant denuded areas heal rapidly without appreciable scarring. Unlike pemphigus vulgaris, mucosal lesions occur infrequently. Bullous pemphigoid is a chronic, recurrent but self-limited disease, and adequate control is usually achieved with doses of a systemically administered corticosteroid far smaller than those required to suppress pemphigus vulgaris.

The identification of an antibody specific for the basement membrane zone of stratified squamous epithelium excited great interest because the bullous pemphigoid bulla is subepidermal in location, and antibody appears to fix at the site of the primary pathologic lesion. This antibody is demonstrable as a fluorescent linear band of gamma-globulin bound to the dermoepidermal junction and is virtually always of the IgG class. Circulating skin basement membrane zone antibody is also detectable in the serum. Preparations stained with fluorescein-labeled anti-B_1C indicate that complement is bound as well at the same site in affected skin. Occasionally patients with bullous pemphigoid have failed to show antibody in both tissue and serum,[47, 49] but absence of antibody in the tissue has been attributed to loss of both antigen and attached IgG as a consequence of severe inflammation and is said to be obviated by obtaining tissue from fresh and early lesions for immunofluorescent preparations. As in pemphigus, the quantity of antibody may be titered, but in bullous pemphigoid the titers are said to correlate less well with the severity of the disease.

The occurrence of both fixed and circulating antibody to the skin basement membrane zone has not been observed in patients with any other disease.[47, 49] Cutaneous tissue from patients with lupus erythematosus also shows staining of the basement zone with the direct immunofluorescent technique, but the band is usually granular in appearance and interrupted rather than linear. Circulating anti-basement membrane zone antibody is never detectable in lupus erythematosus.[65]

The significance of pemphigoid antibody, like that of pemphigus and dermatitis herpetiformis, is still speculative. It is disease specific, localizes to the exact site of the clinical lesion, and can be classified as an autoantibody. Sams[66] has offered a theoretical model of the disease in which the pemphigoid antibody initiates the pathologic process in skin by fixing complement which, in turn, causes chemotaxis of polymorphonuclear leukocytes. He further postulates that release of lysosomal enzymes from the polymorphonuclear cells of the inflammatory infiltrate results in dissolution of the epidermal anchoring fibrils, thus destroying the attachment of the epidermis to dermis. Accumulation of tissue fluid in this cleavage plane would give rise to the blister. There is some precedent for this proposed sequence of events in the pathogenetic mechanism thought to obtain in serum sickness and nephrotoxic nephritis, clinical counterparts of the Arthus reaction.

Attempts to transfer bullous pemphigoid to Rhesus monkeys with high titered serum from humans with the disease have not been successful.[67] Antibody was detectable in the skin basement membrane zone of the injected experimental animals within 3 hours after transfusion, but no clinical or histologic lesions were produced. Traumatizing the skin at the time of maximal antibody binding was also ineffective in producing lesions. Failure to create an animal model may be attributable to species differences, inadequate levels of antibody, or the brief duration of exposure.

Obviously, there are still large gaps in our knowledge of the pathogenesis of bullous pemphigoid. Perhaps if the specific antigen can be recognized the role of the pemphigoid antibody in the disease process can be more appropriately delineated.

Lupus Erythematosus

For over a decade lupus erythematosus has been regarded as the prototype of autoimmune disease. This view has derived support largely from extensive investigations of the renal aspects of the disease. Although three forms of lupus nephritis have been delineated on the basis of light and electron microscopic findings, all are characterized by glomerular and vascular deposition of immune globulins and complement demonstrable by immunofluorescence.[68, 69] Soluble complexes, probably of DNA and anti-DNA antibodies combined with complement are probably responsible in part for the renal damage.[70]

A great diversity of antibodies have been detected in patients with lupus erythematosus.[70, 71] These include lupus erythematosus factor, organ-specific antibodies, circulating anticoagulants, antibodies against formed elements of the blood, rheumatoid factor, and cryoglobulins. Antibodies also occur against nuclear antigens such as double-stranded (native) DNA, denatured DNA, RNA, histones, extractable nuclear antigen, and saline-soluble nuclear component.

Cutaneous lesions are one of the most common manifestations of lupus erythematosus, as they occur in approximately two thirds to three fourths of patients with the disease.[71] Furthermore, unlike the lesions in certain other tissues (e.g., kidney), which tend to be present only in the more serious forms of the disease, skin components bridge the entire lupus spectrum from mild to severe and, indeed, may be the only manifestation in the most benign form of the disease, discoid lupus erythematosus. Therefore, the demonstration by Burnham et al.[72] of a specific immunofluorescent pattern in all types of skin lesions from patients with lupus erythematosus was not only of tremendous diagnostic importance but also of interest in terms of an understanding of pathogenetic mechanisms. On staining with the direct immunofluorescent technique, a band of gamma-globulin can be detected at the dermoepidermal junction. The band is predominantly IgG, although IgM and IgA can be found, and complement (B_1C, B_1A) is usually detectable as well in most of the tissue sections. Several band patterns have been described, including homogeneous, thready, stippled, or various combinations of these.[73] Approximately 90 per cent of specimens obtained from skin lesions of either discoid lupus erythematosus or systemic lupus erythematosus will show the characteristic fluorescent pattern. Sixty per cent of biopsies from uninvolved skin of patients with systemic lupus erythematosus also will have a positive immunofluorescent band, a finding of considerable diagnostic importance. Uninvolved skin from patients with discoid lupus erythematosus has not shown fluorescence.[74]

One of the questions raised in early studies was the possible relationship of the immunofluorescent findings in lupus erythematosus to those in bullous pemphigoid. In both diseases one finds immunoglobulin, predominantly of the IgG class, and complement fixed to the skin basement membrane. However, the morphology of the staining patterns in the two diseases is somewhat different, in that the immunofluorescent band of bullous pemphigoid is tubular rather than granular as in lupus erythematosus.[75] Furthermore, the bullous pemphigoid patient has circulating antibody to skin basement membrane zone, an immunologic phenomenon which is not present in lupus erythematosus. The circulating anti-nuclear antibody in the serum of lupus patients is, conversely, not seen in bullous pemphigoid.

Attempts to correlate the presence of an immunofluorescent band in the clinically *normal* skin of patients with systemic lupus erythematosus with the severity of their disease have yielded varying results. Burnham and Fine[76] found more severe disease, a higher incidence of certain laboratory abnormalities, and more frequent kidney and lung involvement in these band-positive patients and concluded that positive immunofluorescence of uninvolved skin was a poor prognostic sign. In contrast, Caperton et al.,[77] in a small series of patients with lupus erythematosus, were unable to correlate the presence of a positive immunofluorescent band in uninvolved skin with either the severity or type of glomerulonephritis in these individuals.

It is still unclear whether or not the immunoglobulin-complement deposits at the basement membrane zone play a primary role in the pathogenesis of the skin lesions. Presumably, the bound IgG represents either antibody to basement membrane components or part of a circulating antigen-antibody complex with an exogenous or autologous antigen. Both antinuclear and antibasement membrane antibodies have been identified in eluates from the skin lesions of lupus erythematosus.[71] But, until the exact sequence of events in the evolution of the skin lesions is further clarified, the immunofluorescent band test will remain simply a useful diagnostic laboratory finding.

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A Current View of Urticaria

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In an earlier review of this subject,[122] we referred to "The *Vexing* Urticaria Problem," an expression which has subsequently gained rather wide usage. There are many factors which seem to be involved in causing hives in *some* patients, and yet no specific cause can be delineated in the large majority of cases of *chronic* urticaria. Additional comprehensive reviews of the subject have been published in the past by Beall[9] and by Thompson,[133] and there have been more succinct summaries in the relatively recent literature.[23, 38, 40, 82, 85, 107, 121] In the attempt to put the subject into proper current perspective, this article emphasizes potentially relevant pathogenetic mechanisms discovered and published since Thompson's 1968 review. Although some lingering and recent misconceptions must be corrected, it is fortunate that in spite of many fundamental uncertainties, most patients can be managed symptomatically with some degree of success. Angioedema which accompanies urticaria and is thought to be of similar pathogenesis will also be considered here. The hereditary forms of angioedema not accompanied by urticaria will be listed, but not discussed.

The scope of the clinical problem is substantial: it is estimated that probably more than 20 per cent of persons in the United States experience at least one episode of urticaria and/or angioedema during their lifetimes. At one point in time, 0.11 per cent of the males and 0.14 per cent of the females in a survey of 36,475 persons in Sweden objectively exhibited hives.[49] Chronic urticaria occurs most often in young adults, especially women. Some statistics indicate that hives occur with significantly greater frequency in those with a personal or familial history of atopic disease, but they commonly are encountered in patients without such a background. Probably some forms of urticaria are related to atopy and others are not (see below). Among those afflicted, the spectrum of disease ranges from a few, occasional hives of trivial importance to persistent, chronic urticaria, which can be very distressing. Severe, acute forms can be fatal if accompanied by laryngeal edema or anaphylactic shock. The disease is important for the additional reason that it may be a harbinger or indicator of a significant underlying disease process. Conceptually it is receiving increasing attention from those studying mediators of vascular permeability and of the early phases of inflammation.

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PATHOGENESIS

The histopathology of urticaria is quite unimpressive: edema, dilatation and engorgement of minute cutaneous blood vessels, dilated lymphatics, and a meager cellular perivascular infiltrate which may contain some eosinophils. The upper corium is most involved in urticaria, whereas more deeply situated vessels are affected in angioedema. Somewhat surprisingly, electron micrographs of dermographic wheals presented by Cauna and Levine[22] show morphologic changes in the epidermis and some sensory nerve endings, as well as mast cell alterations.

Physiologically, little can be added to Sir Thomas Lewis' observations of almost a century ago[71] indicating a triple response involved in urtication: erythema, wheal, and flare. These gross phenomena result from dilatation of capillaries and venules, increased permeability of the involved vessels, and dilatation of surrounding arterioles caused by an axon reflex. In the ensuing years the essential correctness of Lewis' deductions has been confirmed by others using more sophisticated techniques, such as cutaneous microscopy and experimental injection of dyes or fluorescent compounds into urticating patients.

Lewis recognized that the triple response could be elicited by a wide variety of physical and chemical means, but the capacity of intracutaneous histamine injections to mimic these reactions focused attention on histamine as a potential mediator of urticaria in general. Much subsequent work supports the hypothesis that in many forms of urticaria histamine is released from its storage depots in cutaneous mast cell granules and circulating basophils. One might expect that plasma histamine would be elevated, but this generally does not occur due to the extremely rapid rate at which released histamine is taken up by various tissues.[9] An exception is acquired cold urticaria where histamine is not generally released from the circulating basophils, but there may be such a massive histamine release from the skin of a chilled extremity that local, transient plasma hyperhistaminemia and increased urinary histamine[13] can at times be detected. Changes in whole blood histamine are accompanied by parallel changes in the number of intact basophils.[109] In urticaria pigmentosa or systemic mastocytosis, the enormous increase in histamine turnover permits recognition of the small amount of released histamine which is excreted as such in the urine.

There is much current interest in whether urticaria can be mediated by other endogenously liberated substances, such as serotonin, bradykinin or other kinins, slow-reacting substance of anaphylaxis (SRS-A), or some of the prostaglandins. The first of these is very unlikely to be of major importance in man, since human mast cells are essentially devoid of serotonin. It has been reported that bradykinin can be recovered from dermal perfusates from the region of different types of urticating lesions.[30] However, there is a distinct possibility that the kinin system was activated *after* leakage of the kininogen precursor from the intravascular compartment, and some observers have questioned the identification of the recovered material as bradykinin.[15] A strong possibility remains, however, that kinins may be important in some forms of *angioedema.*

Kallikrein, the enzyme which splits bradykinin from its kininogen substrate, is said to produce larger than normal skin test reactions in patients with chronic urticaria (except for those whose hives are exacerbated with aspirin), but these test sites do not itch.[59, 82, 83] The possible role of SRS-A appears not to have been thoroughly evaluated, though its capacity to produce increased vascular permeability has been documented in some species. Prostaglandin E_1 has a potent and prolonged vasodilating effect in human skin, but the reaction is not accompanied by itching or inhibited by antihistamines.[60, 128] As discussed below, acetylcholine may well play a role in some forms of urticaria, but it may act through histamine release. There is good evidence that anaphylatoxins also act in this manner.[16, 29] A central role for histamine in mediating urticaria is supported by its capacity, intracutaneously, to mimic the pruritus and flare of spontaneous hives. Nevertheless, there is a distinct possibility that more than one mediator might be involved or that there may be interactions among mediators. Particularly suspect is histamine activation of the kinin system through increased vascular permeability.[36, 82, 83]

The major issue relating to the pathogenesis of urticaria is why histamine (and perhaps other mediators) is released at the sites of these lesions. Since it was known even in Lewis' day that histamine is liberated during certain immediate type hypersensitivity reactions, the deduction was made that hives *must* result from allergy. This misconception completely dominated the clinical evaluation of urticaria until about the time of World War II,[20] and unfortunately remnants of this thinking still linger on. Figure 1 presents a scheme of the multiple factors, non-immunologic as well as immunologic, which may be involved in urticaria. One example of the former is cholinergic urticaria – hives coming on after heat, exertion, or emotional tension.[44] In one way or another acetylcholine derived from cutaneous cholinergic nerve endings seems to be involved, perhaps with histamine release as a final step in the process. However, Illig's reported success in transferring this type of reactivity by the Prausnitz-Küstner (P-K) test in a single case suggests that immunologic factors could be involved in some instances.[53] Simple physical or chemical trauma to the skin can produce urtication, e.g., welts after whiplash or after rubbing the lesions of urticaria pigmentosa. Nevertheless, immunologic mechanisms must be considered in those forms of "physical allergy" in which the abnormality can be transferred to normal individuals by serum immunoglobulins.

Pharmacologists have long been aware that a wide variety of relatively simple chemical compounds can release histamine by mechanisms not known to involve immunologic processes.[97] One category of these chemical histamine liberators consists of organic bases which may displace histamine from ionic binding with heparin, an acidic compound, in

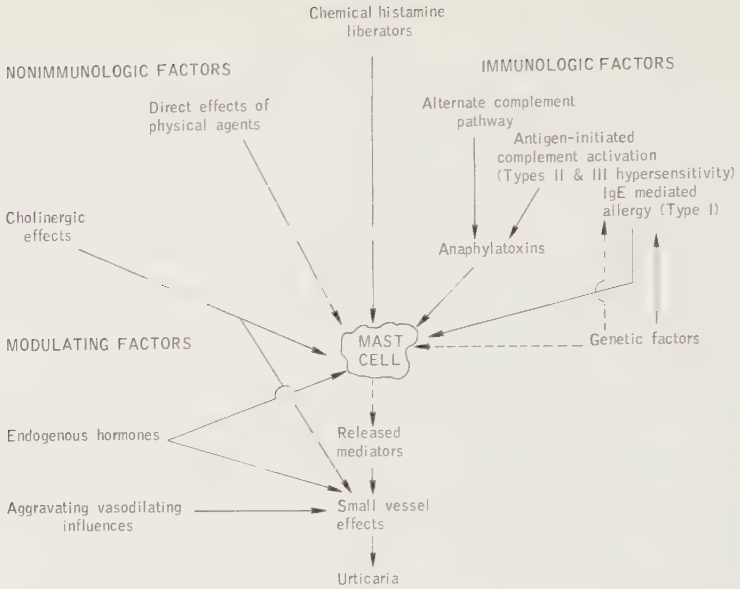
Chemical histamine liberators
NONIMMUNOLOGIC FACTORS
IMMUNOLOGIC FACTORS
Direct effects of physical agents
Alternate complement pathway
Antigen-initiated complement activation (Types II & III hypersensitivity)
IgE mediated allergy (Type I)
Cholinergic effects
Anaphylatoxins
MODULATING FACTORS
MAST CELL
Genetic factors
Endogenous hormones
Released mediators
Aggravating vasodilating influences
Small vessel effects
Urticaria

Figure 1. Schematic representation of factors involved in the production of urticarial lesions.

mast cell granules. Some other histamine liberators are of relatively high molecular weight (e.g., some dextrans, ovomucoid). Recent information supports the need to consider activation of the alternate complement pathway by such substances. As is well known, the family of chemical histamine liberators includes many drugs commonly used in clinical practice, such as morphine, codeine, meperidine, d-tubocurarine, polymyxin antibiotics, thiamine, and stilbamidine. In suitable concentrations such drugs produce wheal and erythema skin reactions in normal subjects (and thereby incidentally provide positive control substances for skin testing). Hives or even shock is especially apt to occur if these drugs are given inadvertently to patients with urticaria pigmentosa. Perhaps the variable response in other subjects relates in part to the mast cell content of the skin.

Immunologic mechanisms probably are involved more often in acute than in chronic urticaria, though it is difficult to assess this matter accurately since many persons with transient hives produced by foods or drugs probably are not seen by specialists who publish on this subject. The most obvious mechanism involves sensitization of the cutaneous mast cells with homocytotropic antibodies to various ingested, inhaled, or injected allergens. This would be analagous to mechanisms involved in anaphylaxis and atopic diseases such as allergic asthma and hay fever. These Type I hypersensitivity states most often are mediated by IgE antibodies which adhere, via the Fc portion of the molecules, to the cell membranes of mast cells and basophils. When two or more of these antibodies react at the cell surface with the same molecule of polyvalent antigen, histamine and other mediators of immediate hypersensitivity may be released. The details of this process have been reviewed elsewhere,[91] but it is of interest that they do not involve complement activation, and they appear to be modulated by intracellular levels of cyclic adenosine-3′5′-monophosphate (CAMP) and probably by cyclic guanosine-3′5′-monophosphate (CGMP).[64] Nevertheless, serum IgE levels generally are normal in urticaria.[58] IgG levels tend to be elevated in adult patients with chronic urticaria,[105] the other serum immunoglobulin values are usually within normal limits,[105] but low immunoglobulins have been noted in children with urticaria associated with infection.[18]

The possible occurrence of urticaria by mechanisms not requiring IgE is illustrated by type II hypersensitivity reactions involving cytotoxic antibodies. For instance, hives may accompany transfusion reactions where IgG or IgM antibodies react with antigens on red cells. Whereas the entire complement cascade must be activated to produce intravascular hemolysis, urticaria may result from active fragments of intermediate components. More specifically, C3a and C5a are anaphylatoxins derived from the activated third and fifth components of complement, and they can produce histamine release from mast cells.[16, 29] It is also possible that a peptide with kinin-like properties derived from C2 might cause urticaria.

Similarly, the complement system can be activated in Type III hypersensitivity reactions by antigen-antibody complexes as well as by aggregated gamma globulins, including some cryoglobulins. In the particular case of serum sickness, complement activation by antigen-antibody complexes undoubtedly is important in producing vasculitis, but the accompanying urticaria could well be due to the concomitant presence of IgE antibodies to the foreign serum proteins. Indeed, both factors may well be involved, the IgE-antigen reaction serving to localize the soluble complexes in vessel walls by increasing their permeability.[66]

Consideration must also be given to the alternate complement or properdin pathway which bypasses C1, C4, and C2, but activates C3 and the subsequent components of the complement sequence. Since this route still yields the C3a and C5a anaphylatoxins, it also may be germane to urticaria. As mentioned previously, it is possible that some of the higher molecular weight chemical histamine liberators or presently unknown urticariogenic substances will be shown to activate this system and, hopefully, explain thereby some of the presently "idiopathic" cases of hives.

It nevertheless appears desirable to use restraint in speculating about anaphylatoxins as cause of urtication, be they generated during activation of the classic or alternate complement pathways. Although human anaphylatoxin activity can be produced with relative ease from isolated complement components, it has been known for a long time that it is difficult or impossible to generate this activity in whole human serum. This has been explained by the observations of Bokisch and Müller-Eberhard that human plasma contains an alpha globulin inactivator of both human C3a and C5a anaphylatoxins[15] which has properties resembling pancreatic carboxypeptidase B and also inhibits bradykinin. There are additional reasons to be cautious about the assumption that urticaria which is associated with complement activation is necessarily caused by it. For example, in a case of monoclonal IgG cryoglobulinemia where complement activation was clearly demonstrated both in vivo and in vitro,[26] P-K tests with the cryoglobulin were positive when challenged with cold at 2 hours but were negative at 24 hours.[25] Similar results have been reported in two other cases,[102,130] and have been attributed to cryoglobulin aggregation and complement activation by the cold stimulus used to challenge the P-K sites, but they might be due to sensitization of mast cells by IgG reagin-like molecules[76,104,105,132a] (even though most human reagins are IgE). Furthermore, Ishizaka's extensive studies on the permeability-increasing properties of antigen-antibody complexes a number of years ago showed some discrepancies between skin permeability-increasing activity and complement fixability, though in general the two activities were similar.[55] In short, there seems to be little doubt that complement activation may lead to edema formation in some circumstances, but whether it leads to localized pruritic wheals and erythema merits further study.

Besides the primary events which cause urticaria, there are many additional factors which modulate or potentiate the development of hives. Their influence may be conspicuous clinically. Many of these factors dilate small blood vessels in the skin: alcohol ingestion,[114] heat, fever, exercise, emotional stress, and hyperthyroidism.[54] Endocrine factors may explain premenstrual or postmenopausal exacerbations of urticaria. The possibility of actual autoimmunity to sex hormones continues to be reported upon.[39,135] Adrenergic hormones also influence the release of mediators from mast cells,[94] as well as directly affecting vascular structures.

Finally, genetic factors play a prominent role in at least six types of urticaria or angioedema. All of these are relatively rare diseases and all appear to be transmitted as an autosomal dominant. (1) Hereditary angioneurotic edema results from a genetically determined deficiency in an alpha 2 glycoprotein which inhibits both the activated first component of complement, Clr, kallikrein, Hageman factor fragments, plasmin, and activated thromboplastin antecedent. The multiple ways in which this deficiency could lead to episodic angioedema have been reviewed elsewhere;[6,68,101,110,112] it generally is not accompanied by urticaria. (2) Patterson et al. have recently described vibratory angioedema, a condition which begins at birth and is accompanied by the release of an unidentified vasoactive amine;[99] again, urticaria has not been observed in these subjects. (3) A heredofamilial syndrome of urticaria, deafness and amyloidosis has been reported,[4,11,65,91] but the cause is unknown. (4) Familial cold urticaria also involves unknown mechanisms, but it is of interest that intravenous endotoxin inhibits the response to cold.[34,134] (5) In familial localized heat urticaria of delayed type, acetylcholine release may be an initiating event.[84] (6) Erythropoietic protoporphyria occasionally is manifested by solar urticaria.[103] The genetics of Type I hypersensitivity are discussed in detail in Dr. Cohen's chapter. A patient with an inherited deficiency of C3 inactivator is reported to have nonpruritic urticaria, occurring particularly after taking showers.

DIAGNOSIS

Recognition of urticaria seldom presents a problem. Particularly characteristic is the relatively brief duration of the individual skin lesions, though the skin as a whole may be afflicted continuously, or episodically, as new crops of skin lesions arise; pruritus of varying degree is almost always present. Angioedema usually is associated with little or no itching, but it can be distinguished from the other forms of edema by its circumscribed nature, usually asymmetric distribution, recurrence in different areas, transient occurrence, localization usually not confined to dependent areas, and frequent association with urticaria or involvement of mucous membranes, particularly of the gastrointestinal tract.

To make the diagnosis of urticaria is usually easy; to determine its cause, while simple at times, is not infrequently difficult or impossible. There are, however, a few varieties of urticaria which can be identified by the appearance of the skin lesions: (1) Cholinergic urticaria has small (1 to 3 mm.) wheals surrounded by a large area of relatively intense erythema in which, at times, satellite wheals may be located. (2) Papular urticaria is characterized by unusually persistent lesions located most often on the lower extremities of children and, by and large, is caused by insect bites (flea, mite, bedbug). (3) Dermographism tends to result in linear wheals in areas of friction with clothing or where scratching has occurred. However, in rare instances linear wheals also may be due to contact with marine organisms (see below), migrating subcutaneous parasites (strongyloides, hookworms), or botfly larvae.[117] (4) In urticaria pigmentosa, wheals occur in areas of trauma to the cutaneous benign mast cell tumors which characterize this disease. These pigmented macules or papules are seen most often in childhood, and the diagnosis is confirmed if rubbing the lesions produces urtication (Darier's sign).[114] (5) Yellowish hives may occur in association with hepatitis, sometimes before jaundice is obvious.[73]

In the large majority of cases where inspection of the lesions is not helpful, the following etiologic factors need to be considered.

DRUGS. Penicillin still heads the list of the innumerable drugs, or their metabolites, which can produce urticaria on an allergic basis. Biologicals which have recently been reported to produce hives include plague vaccine,[106] measles vaccine,[146] and cryoprecipitated human factor VIII.[2] Other drugs which are chemical histamine liberators have been previously mentioned. In addition to being a primary cause of hives,[118] aspirin is an exacerbating factor in many cases of chronic urticaria,[56, 87] so much so that some authorities recommend withholding aspirin from patients with hives.[37] Recognition of a drug as the etiologic agent in urticaria is based primarily on a very thorough history of all drugs taken by all routes prior to the onset of hives, the time relationships involved, history of known prior drug sensitivities, and seeing if the urticaria abates on stopping suspected drugs.[123] More objective confirmation of the diagnosis is often difficult to achieve, partly because metabolites or degradation products often may be the true allergens. Scratch or intradermal skin testing generally is helpful only with high molecular weight biologicals and in penicillin allergy.[69, 138] Several in vitro tests are under evaluation, but most of these are not available for routine clinical use.[79, 108]

FOODS. In the community as a whole, foods probably are a relatively common cause of acute, transient urticaria, most often on an immunologic basis (though some foodstuffs may contain chemical histamine liberators[97]). Obvious examples are hives from various nuts, sea foods, fish, peanuts, eggs, and fresh berries. Fairly often there are accompanying gastrointestinal symptoms, and atopic individuals probably are more likely to have such difficulties. Not infrequently the patient himself makes the diagnosis. As a cause of chronic urticaria of occult etiology, however, most observers have rarely been able to implicate food allergy.*

In cases of recurrent, acute urticaria, a useful initial diagnostic procedure is to have the patient keep a retrospective diary of foods eaten before each episode, looking for a common denominator. With frequent or continuous symptoms, a brief (e.g., 1 week) trial of a rather rigid elimination diet may be useful, with subsequent readdition of foods one at a time.[123] Skin tests are rarely helpful, being positive in acute cases where the clinical diagnosis is obvious and often negative in situations where help is needed. Besides protein antigens in foods, one also needs to consider sensitivity to food additives, such as tartrazine and benzoic acid derivatives.[63]

INFECTION. Several types of association of urticaria with infection have been suggested. Parasitic infestations can be associated with urticaria, and should be suspected in the presence of pronounced eosinophilia or very high IgE levels. Implicated organisms include particularly ascaris, but also hookworm, strongyloides,[28] schistosomes, echinococcus, filariasis,[126] Giardia, amoebae, and malaria. Nevertheless, urticaria in parasitic infestations is infrequent, even in heavily infested patients in the tropics.[96]

Acute viral infections may be associated with hives. Allergy to medications taken for the infection must be ruled out, and fever may be an exacerbating factor. In addition, however, clinical observations suggest a more direct relationship to several viral diseases, such as hepatitis,[3, 67, 72, 73] infectious mononucleosis[1, 27] and Coxsackie infections. The occurrence of urticaria, other rashes or arthralgia in the prodromal phases of hepatitis suggests the possible participation of antigen-antibody complexes as a pathogenetic mechanism.[3] It is tempting to speculate that a response to viral infections may account for a number of "idiopathic" cases of hives.

Chronic focal bacterial infections were strongly emphasized as a cause of urticaria several decades ago, but documentation of an etiologic association generally was not impressive. To the contrary, Rorsman found infection in the oral cavity in 63 of 96 patients hospitalized for urticaria, but the hives in only two of these improved after appropriate treatment.[109] It is important to do a complete history and physical examination on patients who have urticaria. Infections which are discovered should be treated appropriately[125, 129] but may well have no etiologic relationship to the patient's urticaria, and elaborate, time-consuming and expensive searches for inapparent infection appear unwarranted from the available information. More recent emphasis on cutaneous fungal infection as a common cause of hives likewise requires further substantiation.[8, 57]

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*See references 9, 20, 23, 37, 38, 40, 47, 109, 122, 133, 137, 142.

PSYCHIC FACTORS. Cholinergic urticaria was attributed to emotions many years ago. Graham and Wolf observed that skin temperature and response to mechanical stimuli increased and the reactive hyperemia threshold decreased under experimentally induced psychic stress.[12] The partial inhibitory effect of hypnosis on direct wheal-and-erythema skin tests and on passive transfer (Prausnitz-Küstner) responses also are germane.[12, 13] However, various investigators have not been able to agree on a personality profile characteristic of patients with urticaria. Although clinical experience makes it easy to accept the concept that emotional stress can precipitate or aggravate hives in some patients, the question of whether this factor *alone* is sufficient to produce urticaria is not yet answered.

INHALANT ALLERGENS. Urticaria from inhalants occurs most often in association with respiratory symptoms following heavy exposure of highly sensitized atopic persons to potent allergens, e.g., animal danders, flour (in bakers), castor bean dust, and fish odors. Occasionally hives occur seasonally during respiratory pollenosis, and rare seasonal cases due to pollen have been reported in the absence of respiratory difficulty.

PHYSICAL AGENTS. While not numerous, intriguing cases of hives due to a variety of physical stimuli comprise a significant segment of individuals afflicted with chronic urticaria (Table 1). Minimal mechanical trauma will produce dermographism (urticaria factitia)[95] in about 2 to 5 per cent of the populace. It is desirable to document dermographism with suitable mechanical devices[35, 74] which semiquantitate the mechanical stimulus, since many persons will urticate after severe skin trauma. Although it is presumed that in most instances simple mechanical disruption of mast cells is involved, it has been known for many years that dermographism at times can be passively transferred by the P-K technique. The recent convincing demonstration by Newcomb and Nelson[92] that IgE can be responsible for this transfer strongly implicates an immunologic mechanism in these patients, though the nature of the antigen is unknown (altered or exposed skin antigens resulting from trauma?). As one might expect, dermographism is especially prone to occur when the number of cutaneous mast cells is increased, e.g., after rubbing localized lesions of urticaria pigmentosa or the skin of patients with diffuse forms of cutaneous mastocytosis. Although most patients with this latter condition have thickened skin with accentuation of the skin folds,[139] the skin may appear normal.[115] Dermographism may follow reaction to drugs, especially penicillin; it is readily induced by applying tetrahydrofurfuryl nicotinate (Trafuril) to the skin;[143] and in rare instances it may occur transiently following exercise[78] or exposure to cold in cold-sensitive subjects.[78, 80] Such patients seem to have "leaky" mast cells.

In cases of delayed pressure urticaria, the deep and painful wheals most often develop about 4 to 6 hours after areas such as the palms, soles,

Table 1. *Physical Agents Producing Urticaria*

- I. Mechanical
  - Dermographism
    - Primary
      - Idiopathic
      - Allergic
    - Secondary
      - Cutaneous mastocytosis
      - Transient forms
  - Delayed pressure urticaria
  - Delayed dermographism

- II. Thermal
  - Cold
    - Acquired
      - Idiopathic
      - Associated with cryoglobulinemia
      - Associated with cryofibrinogenemia
      - Associated with cold hemolysins
      - Transient forms associated with other factors
      - Delayed type hypersensitivity to cold
    - Familial cold urticaria
  - Heat
    - Cholinergic
    - Localized heat urticaria
    - Familial localized heat urticaria

- III. Light
  - Solar urticaria
    - Probably allergic types
    - Associated with abnormal protoporphyrin metabolism
    - Idiopathic types

or buttocks are exposed to pressure, and there may be associated malaise, fever, headache, and mild leukocytosis. Ryan et al. have suggested application of a 15 pound weight to the shoulder, thigh or forearm for 10 minutes as an appropriate diagnostic test.[113] Delayed dermographism in these patients is rare, but in others, immediate and delayed dermographism might coexist.[8] Why mosquito bites swell and itch when scratched days after the bite remains an enigma.[74]

Temperature changes also induce urticaria with considerable frequency. Idiopathic acquired cold urticaria is probably the most common example of this.[5] The diagnosis generally is strongly suggested by the history, and some of these patients have drowned after swimming in cold water. In most cases the diagnosis can be confirmed by applying an ice cube to the skin for 2 to 5 minutes; as the skin rewarms following removal of the ice cube, a wheal conforming to its size and shape develops, with surrounding erythema. Occasionally cold water is a more satisfactory stimulus than ice.[120] Quite often the response can be passively transferred to normals in the P-K test. In some instances IgE is the serum factor responsible for this activity,[51] while in other cases it appears to reside in IgM.[111] In the latter instance the IgM remained fixed to the skin only a relatively short time, and it was suggested that urtication might result from aggregation of these macromolecules after exposure to cold. In the cases associated with IgE "antibodies," it is hypothesized that there is an autoimmune reaction with skin tissue antigens exposed or altered by cold.

The differential diagnosis of cold urticaria includes urticaria which is secondary to cryoglobulinemia, cryofibrinoginemia, or the cold hemolysin syndrome.[90] The former of these is diagnosed by a significant precipitation of cooled serum derived from blood drawn into a prewarmed syringe and clotted at 37°. Urticaria actually is one of the less common clinical manifestations of cryoglobulinemia, which occurs in many connective tissue, hematopoietic, or infectious diseases. However, IgG and mixed IgG-IgM cryoglobulins have passively transferred cold reactivity to normal subjects in P-K tests.[25, 26, 102, 130] Cryofibrinoginemia likewise is often secondary to a variety of malignant, infectious or connective tissue diseases, and only rarely a cause of urticaria. If cold urticaria is associated with hemolysis or cold hemoglobinuria, serologic tests for congenital or tertiary syphilis should be carried out, and the cold hemolysin demonstrated by the Donath-Landsteiner test; there also are nonsyphilitic forms of this disease. In addition, cold urticaria has been reported as a transient phenomenon associated with administration of drugs (e.g., griseofulvin), ragweed extract injections[127] or infection.[90] A delayed type of hypersensitivity to cold where the ice cube test becomes positive at 24 and 48 hours has been reported; the histopathology is suggestive of a tuberculin reaction;[119] reaction to an autoantigen is suggested. Finally, familial cold urticaria really is a misnomer in that the eruption consists of erythematous papular lesions which burn or prickle rather than itch. This rare disease usually begins in infancy, the ice cube test is negative, symptoms are delayed in onset after cold exposure, and the rash is accompanied by fever, malaise, arthralgia and leukocytosis.[33, 134]

As mentioned before, *heat* may be a precipitating factor in the development of hives. If heat is suspected to participate in the pathogenesis of cholinergic urticaria, the diagnosis can be confirmed by reproducing the skin lesions by immersing both legs for 40 minutes in water maintained at about 44°C, or injecting intracutaneously 0.01 mg. of methacholine or 0.001 mg. of nicotine picrate in 0.05 ml. of saline. Localized heat urticaria, the lesions of which can be reproduced within minutes by applying heat to a local area of skin, is rare. Delorme's studies of such a patient who was also sensitive to ragweed suggested that different mediators might be involved in producing the wheals induced by heat and by ragweed extract.[32] Recently localized heat and cold urticaria have been reported in the same individual.[132] In familial localized heat urticaria of the delayed type the sharply marginated wheals appear about 2 hours after local exposure to heat, become maximal at 4 to 6 hours, and last about 12 hours.[84] The condition begins in childhood, and passive transfer has not been achieved.

Urticaria due to light, or solar urticaria, is also relatively rare. Nevertheless, Harber has described six different types based largely upon the wave length of light which elicits the lesions.[18, 52, 75] In two of these, Types I and IV, an immunologic mechanism, presumably of an "autoallergic" type, appears to be involved, and serum is capable of transferring the sensitivity by the P-K technique.[18, 116, 117] Type VI results from a genetic abnormality in protoporphyrin IX metabolism and is diagnosed by finding abnormal protoporphyrin levels in red cells or feces.[103] The mechanism involved in the other types is unknown. The lesions are confined to areas exposed to light, and the diagnosis can be confirmed by reproducing the lesions under controlled conditions of light exposure.[7, 52]

INSECT BITES AND STINGS. Urticaria is a prominent feature of anaphylactic reactions resulting from bee, wasp, yellow jacket, hornet, or other insect stings. While the history usually is diagnostic, insect stings should be considered when one encounters an unconscious patient with urticaria. The extensive information on Hymenoptera allergy has been summarized elsewhere.[98, 123] Papular urticaria as a result of insect bites has been previously mentioned.

PENETRANTS. Substances in contact with the skin can cause urticaria, but "penetrant" is being employed in preference to the more commonly used term, "contactant," since the latter incorrectly implies a Type IV hypersensitivity mechanism, and most of the "penetrants" actually do produce micropunctures into the skin. Perhaps the most familiar example would be the wheals developing at the sites of claw marks after a sensitive patient handles a cat or other mammal to which he is allergic. Aside from the hives resulting from insect bites and stings, as noted above, a number of caterpillars, adult moths, beetles, and tarantulas[24] produce hives in everyone where their hairs, scales, or foot processes penetrate into the skin.

The potent and universal urticating effect of several marine forms, such as Portuguese Man-of-War and sea nettles,[19] is well known. Plants also can act as penetrants, the classic example being the nettle rash. Indeed, the term "urticaria" is derived from *Urtica urens*, the common nettle plant. Handling food may produce hives.[111] If simple chemical substances can penetrate the skin of sensitive subjects, they too can produce local urticaria; for example, a physician highly allergic (Type I) to phenylmercurials developed hives in areas of contact with white coats laundered with an antibacterial fabric softener containing phenylmercuric proprionate.[77] Ammonium persulfate in hair bleach also has produced urticaria.[17] Such lesions may result from substances implanted in patients, such as amalgam fillings or vitallium cups or nails.[81, 131]

CONNECTIVE TISSUE DISEASES. Urticaria in patients with systemic lupus erythematosus and other connective tissue diseases has often been commented upon[31, 133] and attributed, as a rule, to the vasculitis which these patients exhibit. However, the precise incidence and circumstances under which urticaria occurs in these patients have not been well documented.

NEOPLASMS. While it is difficult to prove a cause-and-effect relationship, the association of urticaria with neoplasms has been reported often enough to demand a thorough examination of patients who have urticaria, particularly when it continues to recur. Hodgkin's disease and large carcinomas with central necrosis have in particular been associated with hives; resection of the latter has led to disappearance of the skin lesions. Malignancy must be carefully excluded in patients with cold urticaria associated with cryoproteinemia. Lymphomatous diseases also may be associated with mastocytosis.[93]

GENETIC ABNORMALITIES. Three of the hereditary conditions mentioned in the discussion of the pathogenesis of urticaria have been described briefly above in the section relating to physical agents. In the syndrome of urticaria, deafness, and amyloidosis, the hives often are accompanied by limb pains, malaise, fever and leukocytosis. Other features include nephrotic syndrome, pes cavus, increased sedimentation rate and serum globulins, urinary reducing substance, hyperglycinuria, and maladsorption.[4, 11, 65, 91]

MISCELLANEOUS FACTORS. The modulating effect of vasodilating and endocrine factors on urticaria has already been discussed. A previous report[121] of hives resulting from contact with water (aquagenic urticaria) has been supported by a more recent study.[22a] The lesions are pruritic, perifollicular, pinhead size hives, and are thought to result from the formation of a histamine liberator substance upon the action of water or sweat on sebum. The diagnosis is confirmed by the "tepid towel test" – application for 10 minutes of a towel soaked in room temperature water. Unidentified contaminants produced hives on the *ingestion* of water in two recently reported cases.[100] Urticaria developed in three subjects maintained in a pressure chamber when switched from normoxic helium to normoxic N_2 mixtures at the same pressure; the phenomenon was thought to be consequent to the greater solubility of N_2 in tissues.[14]

DIAGNOSTIC PROCEDURES

In view of the multiple diseases with which urticaria may be associated, it is obvious that these patients merit a *complete* history and physical examination which must include testing for dermographia. Instances where the cause can be suspected from the appearance of the lesions are few, and have been mentioned; limitation of the lesions to exposed areas suggests light or cold as possible etiologic factors.

Further diagnostic tests are selected on the basis of suspicions elicited by the meticulous history. Many of these confirmatory tests, briefly mentioned here, are described in detail in standard texts.[98, 123] In testing for abnormal responses to physical factors, it is important not to challenge the patient during the refractory period which is present immediately after naturally occurring symptoms. Scratch and intracutaneous tests with allergens are likely to be helpful only in the small group of patients where inhalants are suspected. It should be emphasized that a careful history alone is quite effective in ruling out many potential causes of hives in observant patients.

When a thorough history and physical examination fail to provide clues about etiology, as is so often the case in *chronic* urticaria, the physician finds himself in a difficult position. A routine blood count, urinalysis, and panel of screening tests (including tests for liver injury and hyperthyroidism) may provide some measure of assurance that an important underlying disease has not been overlooked. Serum complement levels (e.g., C3 and CH_{50}) would be of interest particularly where cryoglobulinemia or connective tissue disease is suspected.[133] The significance of environmental factors might be explored by having the patient take a short trip out of town or move to a motel for a few days; this is most useful in the patient with continuous symptoms who has not moved about much during his illness. The two factors which are least well excluded by the history, examination, and routine laboratory tests are allergy to commonly eaten foods and intestinal parasites. Accordingly, a *brief* trial of a rigid elimination diet and examination of fresh stools for ova and parasites commonly are undertaken, but, as stated previously, these procedures rarely are rewarding in cases of *chronic* urticaria. It should be recognized that since no cause can be found for chronic urticaria in the large majority of cases, prolonging diagnostic studies beyond a certain reasonable point is likely to result only in increasing frustration on the part of both the patient and the physician.

TREATMENT

Obviously, the most satisfactory treatment for urticaria is identification and removal of its cause. This is feasible when the etiologic agent is a known drug, food, infection, insect, penetrant, or neoplasm and sometimes an inhalant or physical agent. Penicillin-sensitive persons with persistent hives should eliminate dairy products, since they may contain penicillin in small quantities. In cases of papular urticaria due to insect bites, it is advisable to also treat the family pets.[144] The more elaborate precautions for Hymenoptera-sensitive patients are reviewed elsewhere.[98, 123] Patients with acquired cold allergy should be forewarned about the danger of swimming, and ingenuity can be exercised to minimize other types of cold exposure. An explanation of the disease process and its triggers should be helpful for patients with cholinergic urticaria, localized heat urticaria, and dermographism. When dermographism is due to mastocytosis, the patient should be given a list of histamine-releasing drugs to be avoided. Simple precautionary measures may help patients with mild solar urticaria, and sun screen preparations containing para-aminobenzoic acid may protect those reactive to light in the 2800 to 3200 Å wave length range. Titanium dioxide is recommended for longer wave lengths.[75] If emotional factors seem important, supportive psychotherapy may suffice, but occasionally referral to a psychiatrist may be indicated.

When the cause for urticaria cannot be found, *reassurance* is very important in that hives and angioedema tend to give the appearance of being more serious than they are. Of course the patient should be alerted to seek immediate medical attention if swelling in the throat develops, and individuals with chronic urticaria should be followed periodically to reevaluate the possible development of a significant underlying disease. Within these limitations, however, it is appropriate to give strong assurance that in most cases the disease is reversible and will eventually disappear. In learning to live with the disease, the patient should be encouraged to avoid aggravating factors as far as is feasible: alcohol, heat, strenuous exertion, and emotional stress. Although in many instances chronic urticaria cannot be "cured," patients can properly be assured that it usually can be controlled with suitable modifications.

No symptomatic therapy may be required for very mild urticaria of known cause. However, if the cause is unknown or the patient is uncomfortable while awaiting relief following withdrawal of a known causative factor, many types of medications may provide relief of itching and suppression of urtication. Antihistamines probably are the most commonly prescribed drugs. Large doses can be given in acute, severe urticaria, and the more soporific types (e.g., diphenhydramine) may be preferred at bed time or when itching is severe. Intravenous antihistamines may have a dramatic but short-lived effect, and the patient is apt to become very drowsy. Prophylactic administration of antihistamines can be very effective, e.g., before going out into the cold or the sunlight. More recently hydroxyzine (Atarax; Vistaril) has been used increasingly for urticaria. Perhaps because it has multiple pharmacologic properties, it seems at times more effective than the "old-fashioned" antihistamines, and it has a more prolonged effect in inhibiting wheal-and-erythema skin reactions in human skin.[11] In cold urticaria, cyproheptadine (Periactin) has been reported to be especially effective.[140]

Before the advent of antihistamines, ephedrine was used for urticaria, and there are still a few patients who respond to it, alone or in addition to antihistamines. Older controlled studies of the effectiveness of aminophylline in urticaria[21, 136] are likely to receive renewed attention in view of the current knowledge that this drug, as well as beta-adrenergic compounds, can elevate cyclic AMP levels in cells, with associated decreased histamine release. In instances of severe, acute urticaria, especially if accompanied by angioedema, subcutaneous epinephrine remains the drug of choice. Longer acting forms (e.g., Susphrine) may be used if the hives tend to recur rapidly. Tracheostomy or intubation may be required in occasional instances where laryngeal edema does not respond to other forms of treatment. Corticosteroids are generally neither necessary nor desirable in chronic urticaria, but occasionally they are tried in extremely refractory cases. They are more rationally employed in severe, self-limited urticaria, as in serum sickness. Here their use is to be encouraged if there are complications, such as neurologic involvement. Topical therapy is relatively unimportant in urticaria, but if desired, bland, antipruritic topical medications, such as calamine lotion, may be used. Topical corticosteroids are not indicated for hives.

Tranquilizers might relieve anxious patients, and the dual antihistamine and tranquilizing effect is one of the advantages of hydroxyzine. Innumerable other forms of symptomatic therapy have been tried in the past but have not withstood the test of time.[122] It is particularly disappointing that chemical depletion of tissue histamine stores by the histidine decarboxylase inhibitor, brocresine,[70] has not proved to be very effective.[46, 50, 145] The reported usefulness of the kallikrein inhibitor, Trasylol, in chronic urticaria is severely limited by its capacity to produce anaphylactic shock on readministration.[61, 62] Winkelmann feels that the development of chronic urticaria is less likely if symptomatic treatment is maintained for 2 weeks after acute urticaria has resolved.[47, 142] The treatment of anaphylaxis with urticaria is reviewed elsewhere.[98, 123]

Hyposensitization or immunotherapy in general has little applicability to the control of urticaria. Its main indication is Hymenoptera sensitivity.[98, 123] It also can be considered in the rather infrequent cases of seasonal urticaria associated with hay fever or asthma due to pollen. Desensitization to needed drugs has been attempted in rare instances.[98, 123] Although hyposensitization to cold has been proposed by such measures as bathing once or twice daily in water which is decreased in temperature by 1°F daily, experience with this procedure has not been encouraging.

PROGNOSIS AND CONTROL

In most patients with urticaria, the prognosis is favorable except in persons who have a serious underlying disease. Little information has been available about the duration of the disease prior to the survey of patients reported by Champion et al. in 1969.[23] In this series the mean duration of urticaria alone was 6 months; angioedema alone lasted an average of about one year; and urticaria together with angioedema had an average course of about 5 years. These figures might vary depending upon whether one is surveying a community, serving as a primary care physician or engaged in a referral practice at a major medical center. The average duration of cholinergic urticaria has been reported to be over 7 years.[88]

The large number of "idiopathic" cases makes it obvious that clinical understanding of urticaria still is rudimentary. Nevertheless, the identification of definitive clinical entities which include urticaria is giving direction to more fundamental research. For example, it is of interest that urticaria is delayed in onset, may be accompanied by malaise, fever and/or leukocytosis, and is associated with greater than usual cellular infiltrate in the skin in familial cold urticaria, delayed pressure urticaria, and in patients with the familial syndrome of urticaria, deafness, and amyloidosis, and that familial localized heat urticaria also has some of these features. These findings make histamine an unlikely mediator, and the fact that three of these four diseases are inherited suggests the possible existence of a genetic defect, perhaps the lack of an inhibitor to another mediator or its precursor substance, comparable to the defect uncovered in the brilliant and productive investigations of hereditary angioneurotic edema. The clinical observations on hives associated with several virus infections also encourage further exploration for additional cases of urticaria relating to viruses.

Recent basic pharmacologic and immunologic investigations have been fruitful in elucidating interrelationships between the complement, kinin, and plasmin systems.[6] In attempting to relate this work to clinical urticaria, a particularly pressing question at the moment is the role of the complement and alternate complement pathways. While there seems to be little doubt that these systems can lead to edema formation, documentation of their capacity to produce typical pruritic urticaria in man is urgently needed, particularly in view of the active anaphylatoxin inactivator in this species. Increasing knowledge of the processes involved in mediator release from mast cells, including the roles of cyclic AMP and cyclic GMP, should lead to better understanding of how to control this basic event.

SUMMARY

The primary event in producing urticarial wheals appears to be the release of mediators, particularly histamine, from mast cells, though additional mediators may be involved secondarily. Many factors, both immunologic and non-immunologic, may lead to this process. This is reflected clinically by a large diversity of substances which can produce urticaria in individual patients. Nonetheless, no etiology can be identified in a large portion of patients with chronic urticaria, but fortunately urticaria usually can be controlled while the disease runs its natural course. Currently developing information is likely to aid in understanding these vexing cases of idiopathic urticaria.

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Diseases Which Simulate Allergy

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Allergic diseases may be spontaneous or induced, may be IgE mediated, non-IgE mediated, or non-antibody mediated, and may involve any organ system. The number of types of reaction patterns, i.e., "diseases," is therefore quite large. Fortunately, allergic symptoms and signs tend to cluster about certain organ systems; the vascular system, which may show wide-spread involvement although arteriolar disease tends to be patchy, and as a rule normal vessels outnumber diseased vessels; the skin; the eyes; the ears; the upper respiratory tract; the lower respiratory tract; the gastrointestinal tract; and combinations of several or most of these.

The facility with which allergic problems mimic nonallergic disease states has been repeatedly stressed. Unfortunately, the reverse has not been the case, even though the one situation is the mirror image of the other. With the possible exception of Chevalier Jackson's dictum,[1] "All is not asthma that wheezes," the obverse proposition has rarely been emphasized. It can be instructive, at times, to change the usual clinical question from "Are these symptoms and signs due to allergy?" to "What nonallergic diseases or symdromes would cause these apparently allergic symptoms and signs?" In this frame of reference, the major patterns suggesting allergic cause will be considered unless they are discussed elsewhere in this symposium.

THE VASCULAR SYSTEM

Systemic anaphylaxis varies from comparatively controllable erythema, urticaria, and angioedema to profound respiratory distress and failure to peripheral vascular collapse.[2-4]

It is important to recognize that the anaphylactic syndrome can arise without participation of the immune mechanism, since the final common path of the reaction is mast cell degranulation and release of chemical mediators, principally histamine. Numerous drugs and chemicals will accomplish this without a latent period, i.e., with no need for antibody development. Hence, the reaction can, and does, occur on first exposure to many agents. At the time of the reaction, the differentiation between antibody-mediated and non-antibody-mediated anaphylaxis is immaterial. The differentiation can be made later after the patient has survived.

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The three main forms of clinical shock are hypovolemic shock, decreased cardiac output shock, and neurogenic shock.

Hypovolemic shock can occur in generalized urticaria secondary to the sudden massive shift of fluid from the intravascular to the interstitial compartments. Additionally, it can occur with generalized weeping dermatitis because of massive loss of electrolytes and body fluids. Commonly, the former can mimic anaphylactic shock; rather uncommonly, so can the latter.

Decreased cardiac output may occur because of myocardial damage or pulmonary embolism. Myocardial damage rarely presents a differential diagnostic problem in view of the cervical venous distention, gallop rhythm, poor quality heart sounds, and characteristic electrocardiographic changes.

Since wheezing can be profound with acute pulmonary embolus, the chest may be fixed in inspiration, and the patient cyanotic, the second form of anaphylaxis may be mimicked. Differential diagnosis is aided by the circumstances under which the reaction occurs; evidence of deep vein thrombosis; cervical venous distention; profound dyspnea and tachycardia; a loud P_2; hemoptysis; and characteristic electrocardiographic changes; i.e. an S_1 and Q_3 pattern.

Peripheral vascular collapse – *neurogenic shock* – is the most dangerous form of anaphylaxis. Since it is neurogenic, any of the causes of neurogenic shock can mimic the symptoms.

Simple faint is a good deal more common than anaphylactic shock, but, unfortunately, its onset is identical with anaphylaxis. Fortunately, the fainter is promptly revived on assuming the recumbent position; and, within moments, the pulse becomes full and bounding rather than rapid and thready. The response is characteristic; nonetheless, if any doubt exists, it is safer to administer epinephrine immediately.

The circumstances under which vasovagal reflex shock arises – during the course of instrumental manipulation and or several visceral pain – usually allows its differential diagnosis.

Shock from autonomic blocking agents is characterized by the presence of hypotension without the accompanying peripheral manifestations of shock; i.e., absence of tachycardia, cyanosis, sweating, and cold extremities.

Anaphylaxis which is localized in the skin may appear as erythema (in its various forms[5]), urticaria, or purpura. The differential diagnostic problems of this group including nonallergic, nonatopic urticaria,[6, 7] the controversial role of infection,[8] and urticaria caused by cold agglutinins, are discussed in the articles on urticaria and on the allergic potential of the skin.

It might be worthwhile to single out hereditary angiodema because, while rare, it is always suspected by house staff and attending physicians. Characterized by recurring episodes of circumscribed angioedema of the skin or respiratory or gastrointestinal tract, the disease often begins in childhood, and the lesions are often precipitated by trauma. Urticaria rarely accompanies the angioedema, which tends to begin acutely and is usually transient, although the areas of angioedema may persist for several days. Associated abdominal symptoms are frequent and include nausea, vomiting and severe abdominal pain, at times suggesting the need for surgical intervention. Acute laryngeal edema is common, and almost 20 per cent of patients with hereditary angioedema have died in their third decade because of asphyxia from laryngeal edema.

The disease is due to a hereditary lack of an alpha-2-globulin in the serum of the affected patients which normally inhibits the action of complement component-1-esterase.[7] Purified C-1-esterase inhibitor is not yet available; in the meantime, the patients usually respond to the infusion of fresh plasma.

The purpuras represent a more common differential diagnostic problem than hereditary angioedema. Purpuras may be extravascular, vascular (i.e., affecting the wall of vessels), or intravascular; they may be associated with normal platelet counts, or with thrombocytopenia.

Nonthrombocytopenic purpura may be seen in association with other severe cutaneous eruptions, notably erythema multiforme, or may occur as an isolated entity. Isolated nonthrombocytopenic purpura may occur with drug administration, i.e., sulfadiazines, barbiturates, gold salts, carbromal, iodides, antihistamines, meprobamate, thiouracil, phenylbutisone, and others.[10] When articular and gastrointestinal symptoms occur with nonthrombocytopenic purpura, the condition is often referred to as Henoch-Schoenlein (anaphylactoid) purpura.[11] In children, the entity is mainly streptococcal in origin. In the adult, drug etiology should be suspected.

Thrombocytopenic purpura may occur as a reaction to a drug (allergic purpura), but most commonly is due to hypersplenism or idiopathic cause (i.e., idiopathic thrombocytopenic purpura).

Hemorrhagic urticaria always suggests an underlying vasculitis. The pigmented purpuras may be due to such rare entities as Schamberg's disease[12] or to persistent erythema multiforme-like skin diseases; but their presence should suggest underlying vasculitis as well.

THE SKIN

The various forms of allergies of the adult skin are described in the article by Solomon and Esterly. In this area the most common errors occur in the differential diagnosis of the eczemas which, particularly for the non-dermatologist, tend to resemble each other.

Conditions Confused with Contact Dermatitis

The skin conditions most frequently confused with contact dermatitis are the following.

Seborrheic dermatitis. Here erythema is modest, scaling is prominent, and predilection for certain body sites helps to establish the diagnosis: scalp, eye brows, nasolabial folds, intertriginous areas, and intragluteal cleft.

Atopic dermatitis. In this entity, unless secondary infection has occurred, vesiculation is rare; the predilection for the flexural areas is characteristic.

Dyshidrotic eczema. Here vesiculation occurs, but is intraepithelial, tiny, and rice grain in character, as well as uniform in size. Varying size of the vesicle is rarely seen. Erythema may be pronounced, but is usually associated with excessive perspiration and coldness of the extremity concerned.

Herpes zoster. Here the vesicles are tense and on an inflamed base, but the surrounding skin is not characterized by significant erythema. Distribution along the path of nerve distribution is characteristic.

Neurodermatitis. The circumscribed variety is usually characterized by marked lichenification; there is little evidence of vesiculation and/or erythema unless secondary infections occur.

Nummular eczema. The characteristic coin shape, papular character, and fine scale should be sufficiently characteristic.

Dermatophytosis. This becomes a problem when the contact eruption is limited to the feet. In this case, the localization of the lesion is helpful; i.e., dermatophytosis tends to involve the web and plantar surfaces of the feet, whereas contact dermatitis involves the dorsum of the foot and the toes, rarely the interdigital web and/or the plantar surface.

Infectious eczematoid dermatitis. Here the prominence of pustulation, the lack of sharp margination from the surrounding normal skin, and the generally "infectious look" helps to establish the diagnosis.

Disorders Mimicking Atopic Dermatitis

Atopic dermatitis presents differing clinical forms which are associated with various phases of life. Infantile eczema occurs in two forms. The classical form tends to be characterized by erythematous, papulovesicular, moist lesions which are followed by crusting. The face and scalp are usually first involved, followed by spread to the extensor aspects of the extremities, buttocks, and thighs; and lastly the anogenital region and/or trunk. The lesions can be mimicked by: contact dermatitis, seborrheic dermatitis, intertriginous infantile eczema, diaper dermatitis (a form of primary irritant contact dermatitis), and monilial dermatitis.

The nonclassical form, i.e., atopic erythroderma, a generalized atopic eczema of infancy, is characterized by profound itching, erythema, fine scaling, cold blue hands and feet, and marked axillary and inguinal lymphadenopathy. When not infected, this entity can be mimicked by the following.

Seborrheic erythroderma. In this case, the hands and feet tend to be warm and red, and there is little adenopathy present. On the whole, itching is less intense.

Monilial erythroderma is usually associated with thrush; and the presence of thrush is diagnostic.

The ichthyosis syndromes, especially lamellar ichthyosis (collodion baby), characterized by a collodion-like skin covering that dries and peels off in large sheets, and tends to reform repeatedly.

Disorders Simulating Impetiginized Atopic Erythroderma

Impetiginized atopic erythroderma, i.e., the development of secondary infection usually due to streptococci or hemolytic staphylococci, can produce a picture which can be mimicked by a variety of skin diseases.

Leiner's syndrome[13] resembles generalized seborrheic dermatitis with superimposed infection (staphylococci and/or candida), and is now recognized as a C5 deficiency.

Lyell's syndrome (*toxic epidermal necrolysis*)[14] begins around the mouth; spreads in hours to the entire body surface; and is followed by large bleb formation. The least pressure causes the epidermis to desquamate leaving large, red weeping areas (positive Nikolski's sign) with a final picture that resembles scalding; hence, its other name, the scalded baby syndrome. Its cause is staphylococcus aureus phage type 71.

Ritter's syndrome[15] presents the same clinical picture as Lyell's and the two syndromes may be identical.[16]

Bullous ichthyosiform erythroderma occurs in both sexes. Infants are usually normal at birth, but the condition appears within 7 days. Rapid repeated eruptions of bullae are associated with erythema and scaling. From the third month on, hyperkeratotic lesions appear and become prominent by the third or fourth year in the form of warty streaks in the flexural zones. Nails and hair are normal, and general good health is usually preserved.

Juvenile eczema and neurodermatitis. In childhood, the lesions of atopic eczema may be erythematous and papular; more often they are thickened and lichenified. The lesions are usually well marginated and involve principally the antecubital and poplital fossae, followed by the flexural and extensor aspect of the wrists; and less commonly, the dorsum of the hands. The neck (especially the nape and lateral aspects), face and scalp may be involved. The lesions can be mimicked by seborrheic dermatitis, infectious eczematosis dermatitis, xeroderma and ichthyosis, miliaria rubra, or combined lesions. The simultaneous occurrence of atopic eczema, seborrheic dermatitis, and infectious eczematoid dermatitis is frequent. Recognition of the last two components as a complication of atopic eczema is important.

Contact dermatitis frequently occurs as a secondary phenomenon in the treatment of atopic eczema. The sudden "lighting up" of an indolent eczema with erythema and vesiculation suggests this complication or secondary infection. The presence of pustules suggests secondary infection; i.e., impetigination.

Dyshidrosis (*pompholyx*) frequently occurs in association with atopic eczema; and when present, may produce vesiculobullous lesions on the hands or feet.

EYES

Eyelids

Marginal blepharitis. The fine honey-colored scale on the eyelid margins of those with low-grade acute or chronic allergic conjunctivitis is common. Perhaps more common is seborrheic marginal blepharitis in which the scale tends to be a bit more coarse, and more yellow. The association with seborrhea of the eyebrows, of the scalp, or behind the auricle helps to make the diagnosis.

Dermatitis. Atopic dermatitis of the lids can be mimicked by seborrheic dermatitis. Allergic contact dermatitis of the lids can be mimicked by primary irritant contact dermatitis of the lids.

Angioedema. Unilateral angioedema of one lid (which is not uncommon) can be mimicked by proptosis, intraorbital tumor, and trichinosis. Unilateral angioedema of both lids (also not uncommon) can be mimicked by nephritis, nephrosis, trichinosis, intraorbital tumor, and unilateral exophthalmos. Bilateral angioedema of the lids can be mimicked by exophthalmos, trichinosis, and Mikulicz disease.

Conjunctivae

Acute conjunctivitis. Since allergic conjunctivitis, seasonal or perennial, is a form of catarrhal conjunctivitis, all forms of catarrhal conjunctivitis may mimic these entities. On the other hand, the seasonal variety is usually not mimicked by any of them with the possible exception of vernal conjunctivitis; in this case, the cobbling of the lateral third of the upper tarsal conjunctivae and the milk-like conjunctival exudate is characteristic, and should make the differential diagnosis.[17] The various forms of acute catarrhal conjunctivitis include epidemic, mechanical, photophthalmia and chronic catarrhal conjunctivitis. The differential diagnosis is aided by the circumstances under which they arise and a stained smear of the conjunctival secretions.[18] The presence of eosinophils differentiates the allergic from the nonallergic varieties.

EARS

The Auricle and Adjacent Skin

Although atopic dermatitis may involve the external ears, allergic contact dermatitis is the only frequent allergic entity involving the auricle and adjacent skin. When not infected, it can be mimicked by primary irritant contact dermatitis, seborrheic eczema, and aural herpes zoster. When secondary infection occurs, it can be mimicked by infectious eczematoid dermatitis, secondarily infected seborrheic eczema, or impetigo contagiosa.

Canals

Rarely one might meet a case of primary irritant contact dermatitis of the external canal (usually these days from the use of Cerumenex); even more rarely, one may occasionally see a case of allergic contact dermatitis of the external canal caused by applied medication, i.e., dermatitis medicamentosa. There is no doubt that on very rare occasions atopic eczema involves the external ear canal; but it is difficult to document and/or prove. Acute and chronic otitis externa are largely variants of seborrheic dermatitis occurring in the external canal. Rarely, true otomycosis may occur. The entity known as swimmer's ear is an acute otitis externa that is probably due to bacteria and/or viruses.

Recurrent Otitis and Serous Otitis

These entities are commonly associated with perennial allergic rhinitis; but they are secondary phenomena. The entities arise just as frequently, if not more frequently, because of mechanical obstruction to the eustachian tube by edematous and/or hyperplastic nasopharyngeal lymphoid tissue. Possibly just as frequent are those arising because of disordered defenses against infection.

Inflammation of the eustachian tubes and barotitis. These entities may be symptomatic or asymptomatic. Why one patient with no visible air in the middle ear has no complaints at all while another with the same degree of air absorption may complain variously of "stuffed up ear," hearing loss, tinnitus, and at times mild discomfort or pain, is quite puzzling. In any event, although the entities are frequent with acute and chronic allergic rhinitis, any entity which produces edema of the lymphoid tissue immediately adjacent to the orifices of the eustachian tubes may produce the syndromes; and this includes infections, viral (principally the common cold) and otherwise, edema and or hyperplasia of Waldeyer's ring, and, probably, simple edema of that small portion of the nasopharyngeal mucosa overlying the orifice.

Lermoyez' syndrome[19] is extremely rare and is characterized by a sequence of tinnitus and deafness that diminishes or disappears after vertigo becomes established (as opposed to the sequence of vertigo followed by tinnitus and persistent deafness that is characteristic of menière's syndrome); or by manifestations of food sensitivity, particularly urticaria, which often antedates the syndrome. The episodes are episodic, and disappearance of tinnitus and deafness is to be expected with complete return to normal, as opposed to Menière's syndrome, which causes more or less permanent hearing loss and disability.

THE UPPER RESPIRATORY TRACT

NOSE

Rhinitis

The three main allergic entities involving the internal nose are seasonal allergic rhinitis, perennial allergic rhinitis, and perennial allergic rhinitis with seasonal aggravation.

Seasonal allergic rhinitis is so characteristic that few, if any, nonallergic entities can mimic this condition once it is well established. On the other hand, before recurrence during particular seasons is obvious, acute viral rhinitis may, to a certain extent, mimic the symptoms. Viral rhinitis, i.e., the common cold, occurs just as frequently, if not more frequently, in allergic people as in nonallergic people. Under these circumstances the differential diagnosis may be somewhat more difficult. Whatever the symptoms of the common cold, at no stage is itching of the eyes, nose, external ears, hard palate, or between the shoulder blades noted, as is common with allergic rhinitis.

Perennial allergic rhinitis

Some of the non-antibody mediated rhinitides which can mimic perennial allergic rhinitis have been reviewed in Patterson's article. Nevertheless, the more important forms are included here since they lead so frequently to diagnostic misinterpretation.

Vasomotor rhinitis. Here the mimicry is excellent; i.e., the nasal mucosa tends to be pale or slate colored, boggy, and show watery and/or mucoid secretions. Itching, though not prominent, may be present. It is helpful to remember that allergic reactions can come on suddenly; but unless potent medications are used, they rarely disappear suddenly. In the case of vasomotor rhinitis, the symptoms appear suddenly; but very commonly, they disappear just as suddenly. This rapid alternation from full blown symptoms to an essentially normal airway often occurring several times within one or two hours is quite characteristic.

Metabolic and endocrine rhinitis. The "stuffy" nose associated with hypothyroidism is often chronic, recalcitrant to treatment, and indolent; i.e., it does not change rapidly, coming on slowly, and disappearing just as, if not more, slowly. The diagnosis depends on the demonstration of systemic hypothyroidism. The endocrine stuffy noses, i.e., premenstrual stuffy nose, vasomotor rhinitis of pregnancy, contraceptive pill-dependent stuffy nose, and menopausal stuffy nose are usually, although not always, associated with a shiny red, rather than pale, nasal mucosa, and the absence of eosinophils repetitively. At times the diagnosis can only be made by circumstantial evidence.

Atrophic rhinitis. The symptoms may mimic perennial rhinitis, but the findings are entirely different; i.e., the complaint of stuffy nose in the face of a thin atrophic mucosa with a larger than normal nasal airway is quite characteristic. In its advanced stages, ulcers, crusts, and the mucopurulent look to the entire nasal cavity make the differential diagnosis quite simple.

Chronic infectious rhinitis. Whether this exists as a primary diagnosis is debatable, but its association with purulent sinus disease is not uncommon. Unilateral predominance, lack of alternation, and the absence of eosinophils usually make the differential diagnosis fairly obvious.

Topical rhinitis medicamentosa may mimic perennial allergic rhinitis in many respects, but the mucosa is either fiery red (with the milder syndromes) or dead white (with the major syndromes such as the overusage of Privine, Afrin, and/or Otrivine).

Systemic rhinitis medicamentosa. Chronic nasal blockade usually without significant rhinorrhea and/or other symptoms is the main complaint, and a history of reserpine ingestion and/or other antihypertensive drugs such as Aldomet or ganglionic blocking agents suggest the diagnosis. The disappearance of nasal blockade following removal of the agents establishes the diagnosis.

Foreign bodies. The propensity which children have for stuffing chewing gum, beads, etc., into their nose is rather awe-inspiring. This form of a unilateral nasal blockade associated with mucopurulent rhinorrhea which shows no evidence of alternation is not too apt to be confused with the allergic entities. On the other hand, allergic children as well as nonallergic children tend to stuff things in their nose; hence, differentiation may at times be quite difficult.

Cerebrospinal rhinorrhea. This rhinorrhea is watery (as frequently are the secretions of perennial allergic rhinitis), is not associated with significant nasal blockade, and ceases when the patient lies down (there is no postnasal drip). Rhinorrhea begins when the patient first stands up. Sneezing may occur, but it is infrequent. At times the rhinorrhea is so profuse on assuming the upright position that it can be collected in a small beaker and analyzed for protein or sugar; the presence of sugar (which is not present in nasal secretion) establishes the diagnosis. More rarely, methylene blue may have to be injected into the third circulation.

Anatomic deformity. Obstruction of the nasal airway owing to enlarged adenoids, posterior choanal atresia, and/or significant nasal septal deformity is usually fairly obvious. On the other hand, nasal septal deflection is an extremely common entity; and unless the deformity is profound, nasal complaints should not be attributed to it.

Nasal Polyps

Unilateral nasal polyps. Since nasal polyps have to begin somewhere, "allergic" nasal polyposis may be unilateral, initially; but this soon changes, and bilaterality is more common. With this exception, unilateral nasal polyps are usually, if not always, due to purulent sinusitis, mainly of the antrum.

Bilateral nasal polyps. Their pathogenesis is not quite clear. They may occur during the course of perennial allergic rhinitis, but just as frequently in long continued vasomotor rhinitis, chronic purulent sinusitis, and "intrinsic" disease of the upper respiratory mucosa. Those associated with aspirin sensitivity and chronic bronchial asthma are particularly recalcitrant to treatment.[20]

PARANASAL SINUSES

Vacuum barosinusitis. The term is somewhat confusing and not universally accepted. It may occur during the course of seasonal or perennial allergic rhinitis, and depends for its development on the obstruction of the respective sinus orifices, i.e., frontal and maxillary. Since edema of the sinus ostium is a sine qua non of its development, any process producing nasal mucosal edema may produce the entity. On an acute basis, the common cold is, of course, the most frequent offender. On a chronic basis, any of the chronic rhinitides (see above) may be associated with the entity. When symptoms suggestive of vacuum barosinusitis become continuous, endosinus polyposis is suggested. The diagnosis can be made only by x-ray study; and at times lipiodol instillation is necessary.

The vasomotor rhinitis associated with migraine headache or Horton's histamine cephalgia may very closely resemble perennial allergic rhinitis with recurrent vacuum barosinusitis. A family history of migraine or a personal history of childhood cyclic vomiting strongly suggests migraine. The characteristic clustering of Horton's headache and the numerous headaches of short duration are fairly characteristic.

THE THROAT

Acute pharyngitis. This entity occurs in allergic and nonallergic people alike, and seldom offers any differential diagnostic problems.

Recurrent acute pharyngitis with or without cervical lymphadenopathy. This entity is possibly somewhat more frequent in allergic than in nonallergic people, but the difference is hardly striking and cannot be depended upon for diagnosis. The recurrent sore throat without cervical lymphadenopathy which often is associated with perennial allergic rhinitis is presumably a chemical pharyngitis caused by continuous bathing of the posterior pharyngeal wall with the highly alkaline allergic secretion. On the other hand, infectious secretions can produce the same syndrome as can chronic rhinitis or sinusitis of any cause. The presence of recurring lymphadenopathy with the sore throat suggests rather strongly a disordered defense mechanism; and all these entities can mimic this picture (see below).

Chronic pharyngitis with or without cervical lymphadenopathy. The causes of this entity are identical with the causes of acute recurrent pharyngitis; indeed, the second entity is commonly the end stage of the first. Smoker's pharyngitis is the most common mimic; unfortunately, the "characteristic" red cobbling of the posterior pharyngeal wall is at times seen in nonsmokers. Nonetheless, its presence, plus a history of smoking more than half a pack per day, is strongly suggestive of smoker's pharyngitis in the allergic and the nonallergic patient alike.

Pharyngitis sicca. This entity occurs because of nasal obstruction and mouth breathing which occurs because of chronic nasal blockade. It can be aggravated by conditions of low humidity which usually occur during the household heating season. While it is a common concomitant of perennial allergic rhinitis, it is by no means characteristic of this entity and any of the entities (noted above) which can produce nasal blockade, mouth breathing, and, hence, dry pharyngitis.

HYPOPHARYNX AND LARYNX

Epiglottitis. This is an acute, life threatening, infectious disease of infants and children; it is rarely seen in adults.

Acute laryngitis. The form of acute laryngitis called "croup" is frequent in infants and children; it is rarely, if ever, seen in the adult. They are differing expressions of the same lesion, i.e., acute laryngitis, and the lesion is primarily infectious (largely viral, occasionally caused by H. influenzae).

Recurrent laryngitis and its infantile and childhood equivalent, recurring croup, are commonly associated with perennial allergic rhinitis. In the child, it seems to be an expression of descending respiratory tract sensitization, and often heralds the development of bronchial asthma. This is rarely, if ever, the case in the adult. Both entities may be allergic in origin, but are just as commonly an expression of diminished resistance to upper respiratory infections.

Chronic laryngitis (chronic husky voice) is rarely, if ever, due to allergic cause. On the other hand, it must be confessed that the diagnosis of chronic laryngitis is morphologic; and the laryngoscopist often uses the term "allergic laryngitis" for want of a better definition of the morphologic entity. Chronic husky voice can be produced by more important entities including vocal nodules, vocal cord paresis or paralysis, vocal cord polyps, and carcinoma of the cords. For these reasons, direct visualization of the larynx is mandatory.

Laryngeal stridor. This entity, which is frequent in childhood either in its congenital form or in association with the croup syndrome, is seen in the adult only on rare occasions.

In the adult, the acute variety occurs with any form of laryngeal edema; almost universally this is angioedema of the larynx, although at times radiation edema (from radiation about the head and neck) may be responsible. It is surprisingly rare with infectious laryngitis, despite the fact that viral laryngitis is a common entity in adults and children alike.

In the adult, the chronic variety indicates either vocal cord paralysis or new growth of the vocal cord. In the adult, inspiratory retraction of the suprasternal notch, sternum, and/or intercostal spaces is rarely seen; and since the noises are transmitted quite widely, confusion has occurred at times with bronchial asthma.

LOWER RESPIRATORY TRACT

The causes of the symptom wheezing are legion (see Table 1); only more frequent entities can be considered here.

Asthma Versus the Bronchitis-Emphysema Complex

Chronic bronchitis is characterized by recurrent daily cough (for a minimum of 2 months per year, over at least 2 successive years) and the expectoration of mucoid or purulent sputum in the absence of other specific causes of cough such as tuberculosis, bronchiectasis, or cystic fibrosis.[21] The sputum cell type is the polymorphonuclear leukocyte which comprises 70 per cent to 90 per cent of the cells. Bronchial epithelial cells comprise the remainder and are usually devoid of cilia. Eosinophils are usually rare, less than 1 per cent.

As chronic bronchitis progresses, centrilobular emphysema appears, involving mainly the centrally placed respiratory bronchiole. The lesions are characteristically more pronounced in the upper zones of the upper and lower lobes, and are associated with inflammatory changes and fibrosis in the respiratory bronchiole. Increases in residual volume are generally less than with panlobular emphysema, giving rise to the so called "blue-bloater."[22]

Panlobular emphysema is a generalized, diffuse involvement of all of

Table 1. *Causes of Wheezing*

- I. Supraglottic Entities
  - A. Retropharyngeal abscesses and tumors
  - B. Epiglottitis
  - C. Hypopharyngeal foreign bodies
  - D. Fractured thyroid cartilage
  - E. Laryngeal edema
    - 1. Croup
    - 2. Angioedema of the larynx
    - 3. Radiation edema of the larynx
  - F. Acute inflammation
    - 1. Acute laryngitis
    - 2. Diphtheritic laryngitis
  - G. Chronic inflammation
    - 1. Chronic laryngitis
    - 2. Tubercular laryngitis
    - 3. Syphilitic laryngitis
  - H. Laryngeal stenosis
  - I. Paresis of one or both cords
  - J. Foreign body
  - K. Neoplasms
    - 1. Benign
      - a. Polyps
      - b. Nodules
    - 2. Malignant tumors
- II. Infraglottic Entities
  - A. Tracheal
    - 1. Tracheomalacia
    - 2. Tracheostenosis
    - 3. Tracheoesophageal fistula
    - 4. Internal tracheal obstruction
      - a. Endotracheal polyp
      - b. Tracheal stricture (tracheotomy scar)
      - c. Foreign body
    - 5. External tracheal compression
      - a. Anterior mediastinal masses
        - 1. Fibroma
        - 2. Thyroid tumors
        - 3. Massively enlarged lymph nodes (tuberculous, lymphomas)
      - b. Vascular lesions
        - 1. Aortic ring
        - 2. Aneurysm of the aorta
        - 3. Aneurysmal dilatation of the aorta
        - 4. Persistent azygos vein
    - 6. Esophageal foreign bodies
  - B. Bronchial
    - 1. Foreign body aspiration
    - 2. Broncholiths
    - 3. Recurrent acute bronchitis
      - a. With immune-incompetence
      - b. Without immune-incompetence
    - 4. Chronic bronchitis
      - a. With stenosis
        - 1. Tuberculosis
        - 2. Syphilis
        - 3. Unrecognized foreign body
      - b. Without stenosis
        - 1. Smoker's respiratory syndrome

Table 1. *Causes of Wheezing* (Continued)

    5. Acute bronchiolitis
    6. Bronchiolitis obliterans
    7. Asthmatic bronchitis
    8. Bronchiectasis
        a. Kartagener's syndrome
        b. Chandra-Khatarpal syndrome
        c. Squire Jones' syndrome
    9. Cystic disease of the lung
    10. Middle lobe syndrome
    11. New growths
        a. Endobronchial polyp
        b. Carcinoma
    12. Muscular hyperplasia of the lung
C. Pulmonary
    1. Alveolar lesions
        a. Bullous emphysema
        b. Congenital lobar emphysema
    2. Bacterial infection
        a. Tuberculosis
        b. Friedlander's pneumonia
        c. Lung abscess
    3. Viral infections (virus pneumonitis)
    4. Mycotic infection
        a. Histoplasmosis
        b. Actinomycosis
        c. Nocardiosis
        d. Sporotrichosis
        e. Aspergilloma
        f. Toxoplasmosis
    5. Parasitic infestation
        a. Roundworms
        b. Schistosomiasis
    6. Toxic alveolitis
        a. Silo-fillers' disease
        b. Acute berylliosis
        c. Vanadium pentoxide
        d. Osnium tetroxide
        e. Silicosis
        f. Halogens
    7. Allergic alveolitis syndromes
        a. Bronchopulmonary aspergillosis
            1. Helminthosporium
            2. Candida
            3. Alternaria
        b. Bird fanciers' disease
        c. Organic dust syndromes
            1. Farmers' lung
            2. Byssinosis
            3. Maple bark disease
            4. Suberosis (cork workers')
            5. Enzyme (bacillis subtillis) workers' disease
            6. Yarn spinner's disease
    8. Alveolitis syndromes of unknown cause
        a. Pulmonary alveolar proteinosis
        b. Amyloidosis
        c. Sarcoidosis

(Table continues on following page.)

Table 1. *Causes of Wheezing* (Continued)

III. Interstitial Fibroses
    A. Anthrocosis
    B. Silicosis
    C. Hamman-Rich Syndrome
    D. Sarcoidosis
    E. Collagen Diseases
        1. Lupus erythematosus
        2. Polyarteritis nodosa
        3. Scleroderma
        4 Dermatomyositis
        5. Rheumatoid arthritis
        6. Rheumatic fever
    F. Asbestosis
    G. Hemosiderosis
    H. End stage–toxic alveolitis syndromes
    I. End stage–allergic alveolitis syndromes
IV. P.I.E. Syndrome
    A. Transient (Loeffler's)
    B. Prolonged
        1. Tropical eosinophilia
        2. Periarteritis nodosa
V. Vascular
    A. Cardiac failure
    B. Pulmonary emboli
    C. Ayerzas disease
    D. Pulmonary hypertension
    E. Pulmonary artery anomalies (infants)
VI. Congenital defects
    A. Congenital cystic disease of the lung
    B. Congenital lung cyst
VII. Occupational Asthma
    A. Allergic
        1. Toluene diisocyanate
        2. Polyvinyl plastic plasticizers (dibutylphthalate)
        3. Teflon pyrolysis products (i.e., polymer fume fever)
        4. Formaldehyde (phenolplastic, urea and melamine formaldehyde plastics)
        5. Cobalt particles
        6. Nickel carbonyl
        7. Platinum salts (oxides, chlorides, and chlorplatinates)
        8. Amino phenols (ortho, meta, and para)
        9. Chloro dinitrobenzenes
    B. Nonallergic
        1. Polymethacrylate pyrolysis products
        2. Epoxy resin
        3. Monomeric styrene (fiberglass)
        4. Nitrocellulose pyrolysis (nitrogen dioxide)
        5. Hydrogen sulfide
        6. Metal fume fever
        7. Beryllium salts
        8. Vanadium pentoxide
        9. Silicon
        10. Halogen fumes
        11. Formate esters
        12. Organic phthalates
        13. Acetaldehyde
        14. Acrolein (acrylaldehyde)
        15. Ethylene oxide
        16. Aliphatic amines (methyl-, Ethyl-, propyl-, butyl-, diamino-butyl, and trimethyl-amino)

Table 1. *Causes of Wheezing* (Continued)

- VIII. Primary Lesions Outside the Respiratory Tract
  - A. Adjacent Structures
    - 1. Eventration of the diaphragm
    - 2. Acute gastric dilatation
    - 3. Tension pneumothorax
    - 4. Pleural effusion
    - 5. Pleural neoplasms
    - 6. Pulmonary artery anomalies (infants)
  - B. Remote
    - 1. Metabolic
      - a. Hyperventilation
      - b. Pickwickian syndrome
      - c. Mucoviscidosis
      - d. Carcinoid syndrome
      - e. Bronchial tetany
        - 1. Thyroidectomy
        - 2. Infantile hypocalcemic syndromes
          - a. Rickets and osteomalacia
          - b. Malabsorption syndrome
          - c. Hypoparathyroidism syndromes
          - d. Hemorrhagic pancreatitis (Fitz's syndrome)
          - e. Nephrosis (Epstein's syndrome)
          - f. Chelating agents
          - g. Citrated blood
      - f. Addison's disease
    - 2. Cardiac failure
    - 3. Vagal reflex
      - a. Gall bladder calculi
      - b. Nasal and paranasal sinus manipulation

the respiratory bronchioles and alveoli within the secondary lobule of Miller. It may exist without evidence of chronic bronchitis or chronic bronchiolitis giving rise to the so called "pink puffer," whose findings include large residual volume, scant cough, and profound dyspnea without cyanosis.[23]

On the other hand, most patients show mixtures of both types of emphysema; and clear clinical separation of chronic bronchitis with centrilobular emphysema from panlobular emphysema is rarely possible.

Asthma Associated with Recurrent Respiratory Infection

The recurrent upper respiratory infection syndrome occurs in atopic children and adults. It may be predicated on increased susceptibility to infections due to chronic or recurring, excessive mucous secretions and mucous membrane edema. In this instance, the demonstration of a preceding stage of food sensitization, atopic eczema, and/or urticaria, a strong family history of atopy, and the presence of immediate wheal-reacting skin test to inhalant allergens serves to establish the diagnosis. In transitional phase patients, i.e., in children who are losing their primary infantile food sensitivities and acquiring childhood or adolescent inhalant allergic sensitization, immediate wheal-reacting skin tests to inhalants may not be demonstrable. In this situation, it can be assumed that the skin tests will appear in due time if frankly atopic manifestations have occurred in infancy, and there is a strong family history of atopy and no obvious increased susceptibility to nonrespiratory tract infections.[24]

The symptom asthma must be differentiated from the diseased host, the asthmatic. The symptom wheezing may occur on an isolated, acute basis following a wide variety of respiratory tract irritations. It is probably true that anyone, placed in the right situation, will develop wheezing.

It is interesting that wheezing tends to be associated with defective immunologic or non-immunologic resistance of the respiratory mucosa. Known defects include: defective mucous secretions, i.e., deficient secretory IgA and mucoviscidosis; defective ciliary beat, i.e., a ciliary beat-inhibiting factor has been discovered in the serum of patients with the mucoviscidosis and,[25] more recently, aspirin disease;[26] defective mucous membrane – thus far, a specific defect has not been demonstrated; defective phagocyte function, including chemotaxis defects, phagocytosis defects, and defects of phagocytic killing.

The chemotactic defects include the "lazy leukocyte" syndrome;[27] the Chediak-Higashi syndrome,[28] as well as several other diseases associated with abnormal leukocyte migration into areas of bacterial or fungal invasion. Normal leukocyte migration depends primarily on the generation of chemotactic factors from complement components 3 and 5 during complement fixation. A defect in either will result in an impaired inflammatory response.[29]

Hyposplenism. The spleen is apparently largely responsible for the clearance of poorly opsonized particles from the blood stream. The congenital or surgical absence of the spleen may result in diminished resistance to infection, particularly to the pneumococcus, the influenza bacillus, or the meningococcus.[30]

Defects of phagocytic killing. The neutrophils and monocytes from patients with chronic granulomatous disease can ingest, but cannot efficiently kill, certain bacteria and fungi. This inability to kill ingested microorganisms leads to chronic infections with granuloma formation and abscesses throughout the entire reticuloendothelial system. Pneumonia, chronic dermatitis, hypergammaglobulinemia, leukocytosis, and the anemia of chronic infection are also characteristic.[31]

Symptoms usually begin in the first few months of life, but patients may live into their thirties. The more common form is transmitted as an X-linked recessive trait, but either sex can inherit an autosomal recessive form, which may be less severe. Variants of the disease have appeared as acquired defects in adults. Hydrogen peroxide is required for phagocytic killing of bacteria and fungi. The phagocytes from these patients are unable to generate hydrogen peroxide. The diagnosis can be suggested by a screening test which depends on the failure of the leukocytes to reduce nitroblue tetrazolium dye.

The Chediak-Higashi syndrome is characterized by giant lysosomal granules in the patient's leukocytes, which ineffectively release their contents, including peroxidase, into the vacuoles of phagocytosed bacteria.[32]

Defects of humoral immunity. Antibody-deficiency syndromes (B-cell defects) include infantile X-linked agammaglobulinemia; transient hypogammaglobulinemia of infancy; selective IgA deficiency; immunodeficiency with hyperIgM; immunodeficiency (antibody deficiency) with normal or hyperimmunoglobulinemia; other immunoglobulin deficiencies: such as antibody-deficiency with normal IgG and deficiency of IgA and IgM, and isolated IgG or IgM deficiency; and hypercatabolic IgG deficiency, which has been described with myotonic dystrophy and IgM autoantibody to IgG, and as a part of a familial syndrome including skeletal abnormalities, chemical diabetes, and hypercatabolism of albumen.

Acquired hypogammaglobulinemia may be secondary to increased loss resulting from the nephrotic syndrome, protein-losing enteropathy, and exudative dermatitis, or to defective synthesis accompanying lymphoma or chronic lymphocytic leukemia.

Acrodermatitis enteropathica, Blume's syndrome, and pernicious anemia may be accompanied by hypogammaglobulinemia, usually involving all three major immunoglobulins.

Defects of cellular immunity without immunoglobulin deficiency include chronic mucocutaneous candidiasis, thymic parathyroid hypoplasia (DiGeorge syndrome), thymic dysplasia with immunoglobulin synthesis (Nezelhoff syndrome), and secondary cellular immune deficiencies.

Diminished but not completely absent cellular immunity may accompany lymphomas, chronic lymphocytic leukemia, lepromatus leprosy, sarcoidosis, congenital rubella syndrome, primary biliary cirrhosis, and very commonly steroid or antimetabolite therapy. Some patients with these disorders also have a deficient antibody production.

Defects of cellular immunity combined with immunoglobulin deficiency. These may include severe combined immunodeficiency and its rapidly fatal variant, immunodeficiency with generalized hematopoietic hypoplasia (reticular dysgenesis); immunodeficiency with short-limbed dwarfism; and immunodeficiency with ataxia telangiectasia, characterized by partial immunoglobulin defects, most frequently deficient IgA, less commonly deficient IgE and/or IgG, and "blunted" cellular immunity manifested by depressed, but not absent, lymphocyte transformation by PHA, prolonged rejection of skin grafts, cutaneous anergy in most cases, and lymphopenia in some cases, but with no difficulty with monilial, fungal, or viral infections including vaccination.

Immunodeficiency with thrombocytopenia and eczema (Wiskott-Aldrich Syndrome).[6,33a] The syndrome of eczema, thrombocytopenic purpura, and recurrent infections occurs in boys as an X-linked recessive trait. There are associated immunoglobulin defects (deficient IgM, elevated IgA) lymphopenia, blunted cellular immunity, and a propensity to develop malignancy. The antibody response to polysaccharide antigen is abnormal, and recent thinking assigns the basic defect as one of deficient polysaccharide processing.[34]

Mild combined immunodeficiency associated with enteropathy. Intestinal lymphangiectasia is characterized by protein-losing enteropathy, mild fat malabsorption, hypoalbuminemia, edema, panhypogammaglobulinemia, lymphocytopenia, and in some patients, failure to thrive.[35] The disease is due to dilated intestinal lymphatics which permit the loss of protein and lymphocytes into the bowel and lumen. The same condition, usually in a milder form, may be associated with Whipple's Disease, regional enteritis, constrictive pericarditis, or tricuspid regurgitation.[36] When frequent infections occur, they tend to be mild and confined to the respiratory tract in adults; but may be systemic, chronic, and lethal in children.[35,36]

Episodic lymphopenia with lymphocytotoxicity (immunologic amnesia) is a syndrome of recurring, severe bacterial and viral infections, eczema, and episodic lymphopenia. Immunologic findings resemble those of animals treated with antilymphocyte serum. Affected individuals have been capable of initiating primary lymphocyte dependent responses such as skin graft rejection and transformation with PHA; but they have lacked immunologic "memory"[37] so that they do not manifest delayed hypersensitivity reactions to commonly encountered antigens, and no more than short, transient, primary type antibody responses on repeated stimulation with the same antigens. The immunoglobulin levels show a consistent abnormality; i.e., elevated IgA; IgM levels low to absent; and IgG levels normal or elevated.

THE GASTROINTESTINAL MUCOSA AND SMOOTH MUSCLE

A wide variety of "dyspeptic" complaints have at times been attributed to food allergy or food intolerance, with little justification. These include: simple belching, belching, mild abdominal distention, and flatulence, and massive gastric distention and tympanites, at times associated with respiratory distress. All these complaints are due primarily to air swallowing: the first two to simple air swallowing; last one frequently associated with hysterical bloating, pseudocyesis, or positive pressure breathing. Occasionally, it may occur with hypokalemia.

Food Intolerance

Intolerance to foods may be nonspecific, or specific for a particular food (such as egg); for a certain class of foods; i.e., carbohydrates, fats, or proteins, or for a particular food constituent. The manifestations of the food intolerance may be entirely gastrointestinal, entirely remote, or combined.

Nonspecific food intolerance is never predicated on an allergic mechanism, and will not be further considered here.

Food-specific intolerance is largely due to an allergic mechanism or an inherited enzymatic defect.

Intolerance to cow's milk is more commonly due to hereditary lactase deficiency than to an allergic cause, but both are common.[38] The demonstration of positive skin tests in the atopic person supports but does not prove milk allergy. Milk precipitins are so common as to have little value in differential diagnosis.

Intolerance to egg is most commonly due to an allergic mechanism. No enzymatic defect has yet been demonstrated for this specific food intolerance. Nonetheless, it may at times be the only manifestation of a class intolerance, i.e., fat intolerance.

Intolerance to nuts and seeds is almost always due to an allergic mechanism. The only differential point is the nonspecific aggravation of the irritable colon syndrome.

Intolerance to *fish and shellfish* materials must be considered allergic until proven otherwise. Dinoflagellate poisoning such as that associated with the "red tide," mussel poisoning, and the Haff syndrome are acute epidemic phenomena, and do not enter into the differential diagnosis.

The cereal grains include those containing gliadin in significant amount, and those which do not contain gliadin.

The gliadin-containing cereal grains are in descending order of concentration, wheat, oats, rye, and barley. The most common manifestation of this specific food intolerance is the malabsorption syndrome associated with mucoviscidosis (gluten enteropathy).

Cereal grains that do not contain gliadin include corn and rice. The indigestibility of the hull of whole kernel corn is notorious, and accounts for most cases of corn intolerance. On the other hand, allergic reactivity to corn is reasonably frequent, although probably not as frequent as some writers would indicate. Intolerance to rice is often immunologic; other mechanisms probably exist, but have not been well documented.

Beef, lamb, and fowl may be allergic or nonallergic in about equal proportions.

Intolerance to pork material is usually a manifestation of a class intolerance, i.e., to animal fats. Occasionally it may be allergic.

Fruits. Gastrointestinal symptoms occurring after fruit ingestion are usually a manifestation of an intolerance; occasionally they may be allergic.

Vegetables. With the exception of the legumes (principally peanut, occasionally soybean, rarely pea) and less commonly, meal beans (gastrointestinal symptoms occurring after vegetable ingestion are almost universally intolerance. They are very rarely allergic.

Class-specific intolerance

Fatty food intolerance is usually due to gall bladder disease, the postcholecystectomy syndrome, or pancreatic disease. It is rarely, if ever, allergic in origin.

Carbohydrate (polysaccharide or starch) intolerance has on very rare occasions been associated with an allergic mechanism. More commonly, it is due to a specific enzymatic defect; an example is sucrose intolerance, characterized by the appearance in both sexes of diarrhea when exclusively milk feeding is stopped and carbohydrates are added to the diet. The entity is due to a congenital defect of maltase and isomaltase in the intestinal mucosa. Treatment consists of withholding all foods containing sucrose, dextrins, or starch.

Class specific protein intolerance syndromes have not yet been identified.

Food constituent intolerance. Intestinal food intolerance due to specific lipid constituents have not, as yet, been demonstrated.

Carbohydrate intolerances are due primarily to deficiencies of sugar splitting enzymes and include the following.

The glucose galactose malabsorption syndrome affects both sexes, with onset, following the first milk feeding, of watery diarrhea which continues after every milk intake. The diarrhea is not relieved or made worse by glucose feeding. The syndrome is relieved by the removal of milk and all carbohydrate foods except fructose from the diet.[40]

Hereditary alactasia, which is due to a congenital deficiency of lactase$_1$, appears in both sexes with equal frequency, and is manifested by the onset of severe diarrhea after the first milk feeding. Mixtures of glucose and galactose are well tolerated, and the syndrome is relieved by rigid avoidance of milk.

Hereditary lactose intolerance affects both sexes with equal frequency, and appears shortly after the first milk feeding. It is due to a hereditary lactase deficiency, and is relieved by a lactose free diet.

Hereditary fructose intolerance syndrome is due to a congenital lack of aldolase in the liver, and appears when fruit is first added into the diet. The symptoms consist of repetitive vomiting associated with hypoglycemic symptoms—i.e., convulsions and coma.[41]

Galactosemia has its onset in both sexes within a few days or weeks of milk ingestion, and consists of vomiting, diarrhea, dehydration, and hypoglycemic crises. The entity is due to the inability to metabolize galactose because of a congenital deficiency of galactose-1-phosphate uridyl transferase (p-gal-transferase). Treatment consists of a galactose free diet.[42]

Protein constituents. Specific intolerance to peptides and or polypeptides have not been demonstrated, but numerous amino acid syndromes are known. The principal ones affecting the gut are the following.

The Fanconi deToni syndrome affects both sexes; onset is at 4 to 6 months, of recurrent vomiting, fever, polyuria, and dehydration.[43]

Phenylketonuria (Folling's syndrome) affects both sexes, and in early infancy is associated with repetitive vomiting. By age 18 months, seizures occur. If the disorder continues, mental deficiency and eczema appear. It is controlled by a low phenylalanine diet.[44]

Hereditary tyrosinemia—tyrosiluria syndrome affects both sexes between 2 to 8 weeks of life; the acute onset of anorexia, vomiting, diarrhea, fever, lethargy, and bleeding phenomenon includes epistaxis, hematemesis, melena, and hematuria. It is controlled by a low tyrosine and low phenylalanine diet.

Hyperglycinuria—hyperglycinemia syndrome appears within the first few months of life in both sexes, and is characterized by lethargy, episodic vomiting, dehydration, repeated infections, and purpura. Its treatment consists of a low-protein diet.[45]

The Dumping Syndrome

In 20 to 30 per cent of patients who have undergone gastrectomy, the early dumping syndrome may appear. This consists of the appearance, within 20 to 30 minutes after eating, of nausea, at times with vomiting; feeling of fullness; borborygmi; and sudden diarrhea associated with weakness, palpitation, pallor, sweating, faintness, and at times syncope. Although some patients have symptoms after each and every meal, many experience the symptoms only after a heavy meal or with single specific meals during the day.[46] In the latter circumstances, the patient may complain that he has a food allergy. The same is true of the late dumping syndrome, which occurs 2 to 3 hours after eating since, in this case, hypoglycemic symptoms predominate. While it seems unlikely that these symptoms occurring in a patient with gastrectomy would be considered allergic, it has happened.

The Malabsorption Syndrome

Here the term malabsorption refers to a general type of malabsorption, almost always involving lipids and often many other dietary constituents as well. Steatorrhea is a constant finding in these syndromes, which include mainly the following.

The diagnosis of *gluten enteropathy* is established by jejunal biopsy, which reveals typical (but not specific) pathologic changes: absent villi, with a flat luminal surface, lined by short epithelial cells; elongated crypts; infiltration of the lamina propria by chronic inflammatory cells, and the patient's favorable response to a gluten poor diet.[47]

Pancreatic insufficiency, which may be due to end-stage chronic pancreatitis, cystic fibrosis (mucoviscidosis), or rarely, carcinoma of the pancreas, is diagnosed by lack of response to the secretin test[48] and ruling out other causes of malabsorption.

Bacterial overgrowth should be suspected in the presence of previous abdominal surgery, multiple jejunal diverticuli, or scleroderma.

Previous surgical procedures, particularly the Billroth Type II gastric resection and extensive resections of the intestine, especially the jejunum, should be suspected.

Numerous other more uncommon entities may be associated with intestinal malabsorption,[49] but will not be detailed here.

Apparent food intolerance, especially to milk, may be associated with ulcerative colitis, regional enteritis (Crohn's Disease), and chronic ulcerative jejunitis.

Ulcerative colitis is a disease which occurs characteristically in persons of either sex between the ages of 11 and 30 years, and is usually manifested by the passage of bright red blood with each bowel movement; the passage of bloody mucous; and certain systemic symptoms including fever, weight loss, anemia, arthritis, erythema nodosum and, at times, ocular lesions including uveitis, conjunctivitis, and corneal ulcers. Aggravation of diarrhea and bleeding have been reported in association with a wide variety of foods, but the aggravation by milk predominates. Whether or not this is idiosyncrasy or allergy remains indeterminate. In any event, confusion with benign allergic syndromes should not occur.

Regional enteritis may appear at any age, but the average age of appearance is 25. There is a slight predominance among males, and the symptoms are variable according to the anatomic location and the amount of the involvement. The period of onset is usually mild with insidious symptoms including borborygmi, bloating, flatulence, mild abdominal cramps, and mild diarrhea, at times associated with moderate temperature elevations.

There is a slow progression to more severe symptoms. These include pain, involving 85 per cent of the patients. Pain is usually of the peristaltic type with or without diarrhea, but when diarrhea occurs, the cramps do not usually subside following defecation. With more advanced disease, the pain may assume a constant character which, initially, may be localized in the periumbilical region, but may also mimic acute appendicitis. Later on, the pain tends to correspond to the site of the lesion and may involve any abdominal quadrant.

Diarrhea is found in 90 per cent of patients; soft or semi-liquid stools are characteristic. Liquid stools seldom occur, and tenesmus is rare unless perineal lesions have developed.

Fever is not usually accompanied by chills.

Perianal-perirectal fistulae may occur.

Symptoms suggesting bowel obstruction or perforation in the stomach or duodenal areas, nausea, vomiting, and ulcer-like pain may occur.

Melena is seen.

Regional enteritis is associated with multiple systemic manifestations including fever, weight loss, polyarteritis, occasionally erythema nodosum, and pyoderma gangrenosum. The diagnosis is made by characteristic X-ray studies and/or at exploratory laparotomy.[50]

Chronic ulcerative (nongranulomatous) *jejunitis* is associated with all the symptoms and signs of malabsorption syndrome. Its etiology is unknown, but it is distinct from lymphoma, nontropical sprue, and dysgammaglobulinemia. There is a lack of response to gluten-free diets, and a return to normal of the associated dysproteinemia after treatment with corticosteroids. The diagnosis is established by jejunal biopsy.[51]

The extraintestinal manifestations of food intolerance include a wide variety of symptoms which, at one time or another, have been attributed to food idiosyncrasy or food allergy. Food might cause respiratory symptoms, but documentation might be difficult. Food-fear induced hyperventilation seems to be less uncommon than one might think.[52] Lassitude, asthenia, mental torpor, and feelings of anxiety have been attributed to food allergy. The evidence for this is not very strong. Protean symptomatology attributed to food allergy includes those symptoms referable to the autonomic nervous system: pallor, rapid pulse, dilated pupils, and sweating; and those associated with the brain and spinal cord, i.e., somnolescence, stupor, memory loss, behavior change, prostration, muscle twitching, blurred vision, diplopia, speech disturbance, coma, and convulsions. When all of these symptoms are present, fasting hypoglycemia is suggested.[53]

More difficult to differentiate are the nonfasting hypoglycemias including alimentary hypoglycemia, functional hypoglycemia, and the hypoglycemia associated with early diabetes mellitus, since the symptoms here are never so dramatic. In addition, symptoms such as weakness, faintness, nervousness, palpitations, feelings of anxiety associated with hunger, headaches, lightheadedness (but rarely true vertigo) may be present. Profuse sweating, coma and convulsions rarely ever occur; and the symptoms are most apt to appear in the mid morning and mid afternoon. They rarely appear in the late evening hours after supper.

In infants and young children, hypoglycemic symptoms occur without gastrointestinal disturbance in several specific enzymatic defect syndromes.

Galactose and fructose intolerance (Dormandy's syndrome[24]); i.e., convulsions and coma following the ingestion, or intravenous use of, glucose or fructose

Glycogen storage syndromes

Others

The appearance of hypoglycemic symptoms in association with intestinal symptoms such as abdominal cramping, borborygmi, diarrhea, etc., suggest not food allergy, but the dumping syndromes or the Zollinger-Ellison syndrome.

Muscular System. Bouts of generalized weakness have been ascribed to food allergy, but this symptom is more suggestive of myasthenia gravis, familial periodic paralysis, thyrotoxic myopathy, or thyrotoxicosis-associated periodic paralysis. It is probably never an atopic phenomenon. Drug induced dermatomyositis is well known. Atopic dermatomyositis has never been demonstrated. Generalized muscular wasting occurs with many congenital enzymatic defects of aminoacid metabolism, but has never been shown to be an atopic phenomenon. The symptom may, however, be seen as a sequela of the dermatomyositis or Guillain-Barré syndromes associated with drug or serum reactions.

SUMMARY

The differential diagnosis of the allergic diseases, which seems deceptively simple, can be one of the most intellectually challenging and, perhaps, frustrating exercises in the practice of medicine. It is the author's hope that the reader who has had the patience to read this article will have found a small "torch of smoky pine" to light his path "one step across the void."[64]

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The "Classical" Diseases of Allergy

*Max Samter, M.D.**

Some of these reflections on the state of the art are being set down on the plane from Chicago to Tokyo where the Eighth International Congress of Allergology is about to begin. Zurich (in 1950), Rio de Janeiro, Paris, New York, Madrid, Montreal, Florence, and Tokyo: a succession of countries, a succession of speakers, a succession of titles: reading the old programs shows clearly how the direction of the specialty has changed. Since it is not possible to sleep alongside the never-setting sun, an appraisal of allergy at 38,000 feet above sea level is bound to be tempered by perspective.

Landmarks

What are the landmarks in clinical allergy during the past two or three decades, i.e., after the discovery of corticosteroids? In a conversation about architecture a short while ago, Leonhard Currie – then Dean of Architecture at the Chicago Circle Campus of the University of Illinois – said that the age of great architects might be over; that architecture might become a discipline controlled by teams; and that this might well be true of medicine. So many have contributed to our understanding of immune complex diseases, to the identification of chemical mediators, to the application of Sutherland's "second messenger systems" to the possible pathogenesis and treatment of allergic diseases; and even the National Institutes of Health, in awarding grants, is clearly partial to teams. Yet, disodium cromoglycate – if it turns out to be a landmark which seems possible, but is still uncertain – reflects Altounyan's single-handed effort; and the Ishizakas' insistence that their postulated immunoglobulin must exist, has transformed the vague era of the "reagin" to the precise era of IgE.[7] In general, progress has been slow: after a generation, the structure of SRS-A is still unknown; after a generation, we still can only guess why corticosteroids control most of the classical diseases of allergy.

A Statement of Belief

When von Pirquet invented the term "Allergy,"[13] he clearly implied that allergists are clinical immunologists, a credo which has been almost forgotten under the impact of the spectacular growth and the coming of age of experimental immunology. Nevertheless, it is true: the fact that hay fever and systemic lupus erythematosus are clinically dissimilar no longer conceals their pathogenetic relationship. Internists and pediatricians might not agree. When I mentioned during Grand Rounds in 1962 that ulcerative colitis might turn out to be a disease treated by allergists, Dr. Harry F. Dowling, then Chairman of the Department of Medicine, reacted appropriately: "Honestly, Max, if you had ulcerative colitis, would you see a gastroenterologist or an allergist?" Of course, he is right, but for practical reasons, not for reasons of principle. It is for practical reasons that the editor has agreed to edit a volume of what are essentially "atopic" diseases (1) because they are "bread and butter" diseases for allergists and non-allergists alike; and (2) because enough has been learned in recent years about their pathogenesis to justify the publication of a volume which brings diagnostic approaches and clinical handling up to date.

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In singling out this comparatively small segment of clinical immunology for special attention, the editor is not at ease. The assignment has some of the attractiveness of a journey into a more idyllic past, not unlike the attractiveness of steam engines which carry railroad buffs on narrow gauge tracks into hidden valleys: it is fun, but it is not real. Our horizon has changed; and nothing is as it was, only one short generation of allergists ago.

Atopy

In the beginning, "atopy" – a term suggested by Perry and adopted by Cooke and Coca[5] – designated individuals who had the inherited ability to become sensitive to airborne pollen. The discovery of IgE changed the wording but not the meaning of the definition: it now applied to individuals who – possibly because of a postulated but poorly defined mucosal defect – synthesize IgE after exposure to pollen and to an increasing number of other "allergens." For years, the definition remained unchallenged even though it failed to explain common clinical observations. For instance, technicians in laboratories might become sensitive to dander of guinea pigs, rats, rabbits, and dogs, but not to ragweed pollen, even in areas in which hay fever is far more prevalent than sensitivity to animal dander. On the other hand, the hay fever patient, once pollen-sensitive, would remain pollen-sensitive after years of transfer to a pollen-free area even though the half-life of IgE turned out to be days or weeks, not years.

By now, we have learned that not only atopy per se, but the ability to respond to a specific allergen might be genetically determined; and if we consider atopy part of our second line of defense against a hostile environment – a misguided defense, perhaps, but still a defense – we can readily accept the presence of "memory" – cells equipped for immunological surveillance and maintenance of adequate titers of antibody in tissues.

Even today, the patient who has a life-long and often overwhelming sensitivity – associated with circulating IgE and positive skin reactions – to a single antigen, e.g., to crustaceans, defies classification. Can he be atopic, in the absence of *any* sensitivity to common allergens? Some say "yes" and apply the term atopy to any clinical entity which can be traced to IgE, but most of us prefer to limit it to those conditions which have a familial component. Infestation with ascaris and trichinella spiralis might induce synthesis of IgE and massive eosinophilia, but they are non-atopic diseases: the point, however, has not been settled, and our terminology must be tightened.

A description of the sequence of cellular and biochemical events which lead to atopy and atopic disease is beyond the scope of this article, but it might be well to indicate at least some of the problems which are currently under intensive investigation. The genetically susceptible atopic patient exposed to ragweed pollen forms anti-ragweed IgE. The antigenically effective components of ragweed pollen have been characterized; the site at which plasma cells form IgE has been established. Once formed, IgE is released and attaches itself to specific receptors on the surface of mast cells which surround the vascular bed of the respiratory mucosa. Exposure of sensitized mast cells in vivo or in vitro to their specific antigens activates enzymes which induce granules to release their preformed chemical mediators and cause clinical symptoms.

Each mast cell has an extraordinary number, around fifty thousand, of receptors for IgE. The attachment of IgE to mast cells depends on the titer of circulating IgE: Ishizaka has shown that an equilibrium exists between circulating IgE and IgE on mast cell receptors.[6] If a patient is ragweed-sensitive, therefore, so many mast cell receptors are occupied, so many are free; and the titer of circulating IgE might be high. It is virtually certain that this equilibrium is an equilibrium between the Fc fraction of IgE and the mast cell receptors. One might expect that a high titer of circulating IgE inhibits additional sensitization, but this is apparently not correct: a ragweed-sensitive patient exposed to a cat seems to become readily sensitive to it. It is tempting to speculate whether and by what means the new anti-cat IgE displaces some of the pre-existing anti-ragweed IgE, but clinical experience suggests that highly atopic patients, particularly children, continue to develop new sensitivities which coexist with the earlier ones.

The answers should be within our reach: they are important, because it is likely that atopic diseases will eventually be treated by modification of the immunologic sequence or of the nonimmunologic results of antigen-IgE-mast cell interaction. At present, skin tests give us a rough estimate of mast cell involvement. The simultaneous determination of circulating antigen-specific IgE which will soon be feasible, should give us a far better understanding of the dynamics of atopic immunology.

Justifying Omissions

During the planning stage of this symposium, three additional topics were given serious consideration, (1) reactions caused by drugs; (2) food allergies; and (3) psychosomatic components which might complicate allergies in adults. In each instance, the idea was abandoned, but the reason for abandoning it deserves discussion because it sheds light on some nonclassical aspects of the classical diseases of allergy.

1. Reactions caused by drugs – both "true", i.e., antibody-mediated, reactions and reactions which simulate allergies – have been of increasing concern to physicians and patients. Their incidence has increased: this had to be expected because of the continuing development of new drugs as well as of modification of older drugs, because of their worldwide distribution, and because of our general inclination to prescribe drugs more liberally than Osler.[9, 12]

Like pollution, chemicals and drugs contaminate our environment; and while there is consensus amongst the concerned authorities that the effects must be bad and potentially serious, more work must be done to accumulate evidence which supports our emotional assumptions. We need clarification of the antigenic potential of drugs: this information is hard to come by, because it is not, as a rule, the drug per se which is antigenic, but one of its metabolites which qualifies as a hapten, forms covalent bonds with protein or carbohydrate and renders them antigenic.

Interaction of drugs is a comparatively new area of research, but it seems quite certain that competition for the same microsomal enzymes increases the chance that alternate metabolic pathways might encourage the emergence of unusual metabolites and, consequently, set the stage for unexpected immunological events: Cluff[3] has provided convincing evidence that the incidence of side effects of drugs rises in direct proportion to the number of drugs which are taken, simultaneously, by individual patients.

By and large, we are forced to assume that the handling of the metabolic processing of the same drug might change, in the same patient, from day to day; and that – with a few significant exceptions – the development of drug reactions might be a function of the host rather than of the drug. Several good reviews are available. For the purposes of this volume, it seemed more profitable to include the major allergic reactions to drugs with the predominant lesions which they induce: this has been done.

2. Food allergy. While several authors of this volume refer to food allergy as a possible cause of disease, food allergy remains a controversial issue, both on theoretical grounds and because of the current unorthodox approaches to diagnosis and treatment which keep the controversy alive.

We have argued before – when we tried to define "atopy" – that development and persistence of marked sensitivity to a single allergen in an individual who has neither a personal history nor a family history of atopy is probably non-atopic. Multiple allergies to food in young children are usually atopic and often followed, later on, by an allergy to inhalant allergens. Allergy to food is often equated with allergy to inhalants, but the differences between food allergy and allergy to inhalants are sufficiently impressive to warrant careful study. In fact, unlike sensitivity to inhalant allergens, multiple allergies to food tend to disappear; and "rotation" diets[11] have been reasonably successful: one might almost suspect that "memory cells" are ineffective or hardly involved in most allergies to food.

The possibility that recurrent complaints of adults, for instance, urticaria or gastrointestinal disorders, might be caused by food allergy should not be dismissed lightly, even though it is often difficult to prove.

Skin tests are unreliable (probably for the same reason which makes skin tests so unrewarding for the diagnosis of hypersensitivity to drugs) and elimination diets followed by re-exposure to suspected foods are technically demanding, traumatic, and might require hospitalization. Food has strong emotional connotations: the patient's emotional response to even tentative withdrawal of certain foods might in itself endanger the validity of his recorded observations even if withdrawal has only been recommended for the differential diagnosis of some of the enzymatic defects which Dr. Beers describes.

The history of food allergy is dotted with attempts to overcome the subjective description of food-induced changes by objective techniques. Widal's "leukopenic index"[14] and Coca's "idioblapsis"[4] which are still in use are interesting efforts, but are statistically insignificant; Rinkel's disciples continue to apply his "provocation test"[10] – the injection of successively increasing doses of antigen until symptoms occur – which is rarely reproducible, under controlled conditions; and the latest addition to the list, the "cytotoxic test"[2] – which records the motility of leukocytes under the microscope after addition of suspected foods – is untenable for basic as well as for practical reasons. Food allergy needs a chapter of its own: at present, it does not deserve it.

3. The feeling that "psychosomatic components *must* contribute to the natural history of allergy in adults" is clearly expressed in some of the earliest descriptions (mainly of bronchial asthma)[8] and shared by contemporary physicians who prescribe staggering doses of tranquilizers, particularly in allergic diseases associated with pruritus, or in chronic bronchial asthma of uncertain etiology: they are rarely helpful. Yet, "stress and strain" have come under scrutiny as possible risk factors which might explain the increase in incidence of allergic diseases since the beginning of the century; and most of us have called allergic diseases "diseases of civilization" even though every major controlled psychiatric study has concluded that they are not. A lingering doubt remains: if autonomic regulations participate in the pathogenesis of *some* forms of bronchial asthma, of some forms of urticaria, a categorical "yes" or "no" seems premature.

Some years ago, a coalition of psychiatrists and internists designed a protocol to establish the specificity of stress in certain diseases.[1] Perhaps the coalition should reconvene and prepare a protocol for the study of factors which might predispose asymptomatic atopic patients to develop symptoms, or of factors which modify the course of the disease once it exists. If I remember correctly, the earlier study used tapes, but had no access to computers. Computers, properly programmed, can assess the pathogenetic significance of coexisting variables with considerable accuracy so that a future volume of this type could include an essay on the role of the psychiatrist in the diagnostic and therapeutic management of patients who have, or are likely to develop, allergic diseases.

A Statement of Intentions

"Allergy in Adults: Inventory and Outlook" is not a manual of diagnosis and treatment in allergy. Given a basic knowledge of medicine and some specific knowledge of common allergens and of the symptoms which they commonly cause, the diagnosis of allergic rhinitis and bronchial asthma can be readily made by internists, pediatricians, physicians in family practice.

Allergists and clinical immunologists must realize that most of their patients are referred because the referring physician wants information about the *predictability* of the disease. It will no longer be fair to say to a mother: "Your child is allergic, and even though he is not now allergic to a dog, he should never be allowed to have a dog." Mothers will be entitled to a precise answer when they ask: "If he had a dog, will he become allergic to it?" Or, when he has hay fever today, "Will he become an asthmatic 20 years from now?" Or if he has asthma, "Might he have a chance to outgrow it, when he gets older?"

The first question is probably an immunologic question; the second and third questions might be non-immunological, but all three are answerable, even with the still limited techniques which are available to us today. With the proliferation of sophisticated methods for immunologic assays in tissues and fluids, with an array of techniques which test the competence of autonomic regulations and of the vascular bed, the specialty must be prepared to answer these questions if, as a specialty, it is to survive. It is the editor's hope that this volume which says much in the text and a good deal between the lines, will be a step on the way.

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